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In this issue:

The Acquired Immune Deficiency Syndrome

by Dr. F.A. Shepherd and Dr. W.K. Evans

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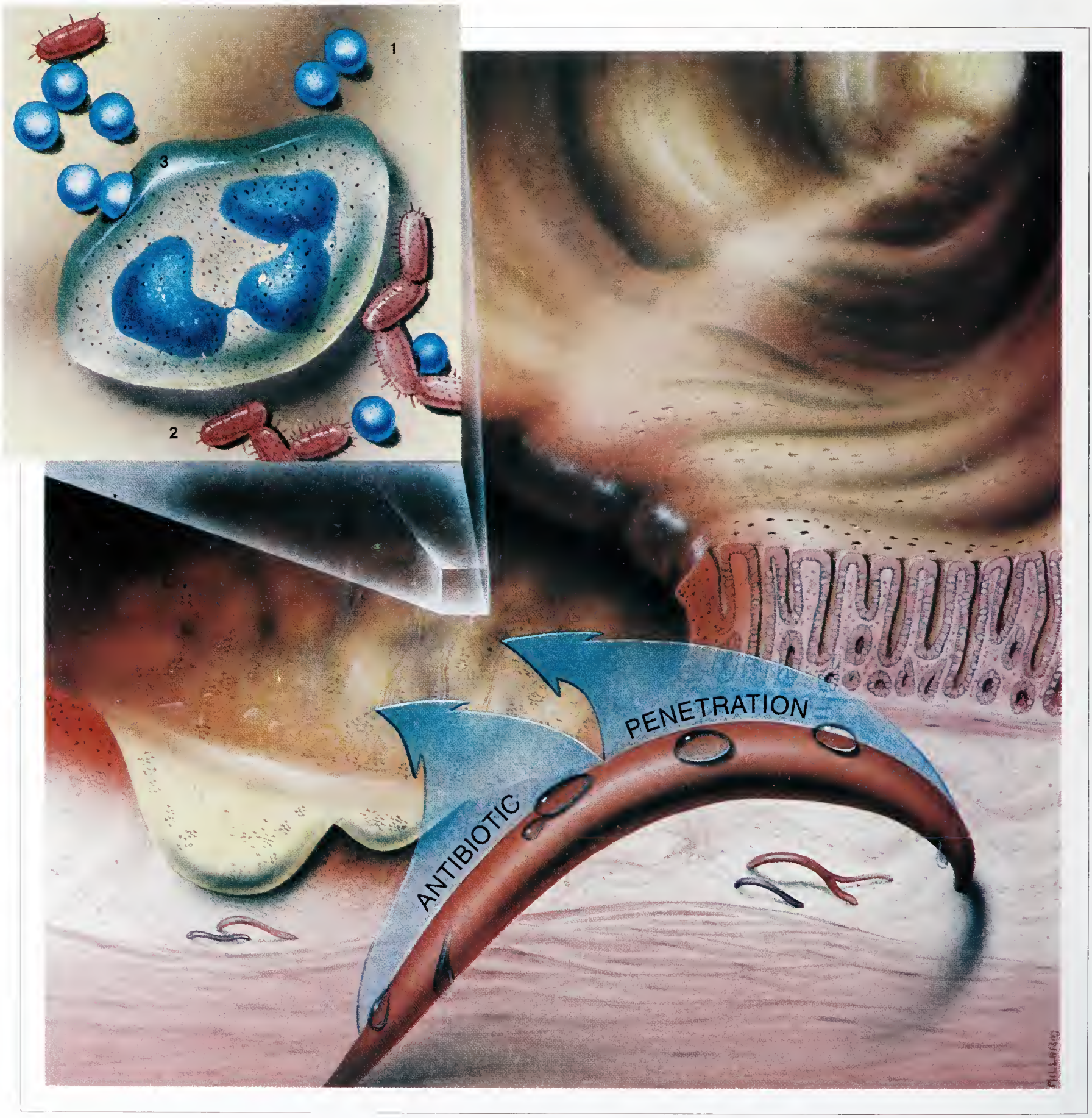

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GUIDELINES FOR PUBLICATION

1) All articles intended for publication should be submitted to the editors before the deadline which is usually six weeks before the release of the Journal.
2) Submitted articles should be typed (or legibly printed) double-spaced, single-sided on paper 8½" x 11" (letter size) and they should not be more than 20 to 30 pages (5000 to 6000 words).
3) Illustrations, graphs, diagrams and figures should be put on a separate sheet and identified by Arabic numerals. A list of explanatory legends for all the figures and diagrams should be put on another sheet. Do not write on the back of photographs.
4) References should be checked with the original sources, designated by raised Arabic numerals in the text, and listed in alphabetical order on a separate sheet. Each periodical reference should include in order: the author's last name and initials, title of the article, journal name, volume number, page number, and year (e.g. Risser JC: Scoliosis: Past and Present. *J. Bone and Joint Surg* 46 A:167, 1964). For further information please consult the MLA Stylesheet.
5) The editors reserve the right to make changes as they see necessary to ensure correctness of grammar and spelling and clarification of statement and conformity. Those views expressed in the commentary do not necessarily reflect the views of the Journal staff.
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The Medical Alumni Association is the bridge between the graduates and the Faculty of Medicine, University of Toronto.

During your undergraduate years, the Association was involved with providing financial assistance (scholarships, bursaries, travel grants, fellowships, loans) as well as sponsoring programs that were of particular interest — General Practice Panel, Arts and Letters Committee, Undergraduate Affairs, Graduation Banquet, etc. Now that you have graduated, the Association is still able to offer financial assistance in form of bursaries and loans; as well as being your representative at the Faculty and University level.

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During the past three years the Association has been involved in collecting funds on behalf of the Faculty of Medicine (Update) to support and expand a Continuing Education program. This program will become increasingly more important if the College of Physicians and Surgeons decides to incorporate the need to re-license physicians every five years. Government funding has been decreased for existing programs, and there is no provision for the incorporation of new ones.

The Association is also involved in providing some impetus to five year reunions. Two letters will be sent free of charge, for each class celebrating their reunion. Every attempt is made to keep an up-to-date address list of all our graduates. Please remember to notify YOUR Medical Alumni Association of any address change.

The Association is governed by graduates who give their time and talent voluntarily. There is one full time employee. Donations given for Student Aid are used entirely for that purpose; and the donations given on behalf of the Faculty of Medicine Update are tuned over to the Faculty without any administrative charge. Trust funds are administered, without charge, following the direction of the donor.

If you are interested in serving on the Executive Committee, or would like to have your opinions voiced to the proper authorities, please do not hesitate to contact YOUR Medical Alumni Association.

Above all, consider it an honour to be invited to attend the Medical Alumni Association and to help those who are coming after you.

MEDICAL ALUMNI ASSOCIATION

EDITORIAL

On Effective Communication

Michael J. Bazos

It is indeed an honor to have the continued privilege of involvement in this year's Medical Journal, the oldest undergraduate publication in Canada, which celebrates its 61st anniversary.

As in previous years, this year's Journal hopes to provide its readers with enjoyable yet relevant articles involving controversial issues facing today's health care team. It further provides a forum of communication whereby undergraduate medical students may share their past and current research activities with their colleagues and teachers.

This issue's feature article presents a literature review on the newly-recognized Acquired Immune Deficiency Syndrome (AIDS). It also mentions some of the unique problems facing medical researchers in attempting to solve this mystery. Those tackling the problem span a broad range of disciplines including immunology, oncology, epidemiology, infectious disease, general practice and social work. In order for this team effort to function effectively, the emphasis of communication and cooperation amongst these medical subspecialties and the community cannot be underestimated. This global network of accurate information exchange is crucial to the efforts of treating the victims of this disease and educating society.

The accompanying article on Kaposi's Sarcoma (KS) discusses a common comorbid condition found in patients with AIDS. It describes the "demographic transition" that has occurred and has compared the insidious European variants of KS with the fulminating African and newly acquired North American forms of KS.

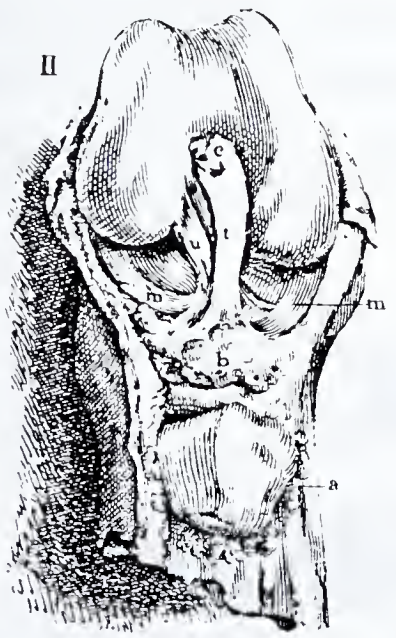
Bernie Boulanger has prepared an excellent radiological review on Hodgkin's Lymphoma with case illustrations utilizing the most up-to-date imaging techniques. This cancer of complex classification shares many B signs and symptomology with KS and AIDS. This suggests a similar viral etiology (e.g. EBV variant).

Dele Davies, Judy Allen and Eben Stern each discuss their research involvements with pulseless disease, orthopedic surgery and wound healing respectively.

Paul Marks stresses the potential gains to be made within the medical profession by understanding and applying computers in medical diagnostics, information storage and medical education. His paper proposes an outline for a course in medical computer applications.

Finally, our commentator, Murray Rosenbaum, takes many of us down memory lane (or for some, future shock) of the "slide-show" lecture series of years one and two. He reminds teachers of the importance of effective communication and cautions students to cultivate their "eye of faith".

In closing, I wish to encourage today's medical students to pursue their efforts in seeking knowledge without fear or shame. We must continue (or for many start) to think and then ask the right questions. Only then can we effectively communicate our understanding to our colleagues and more importantly, to our future patients. That's why we're here! □



THE Anatomy of the knee-joint is continued in this plate. It explains the internal parts, the knowledge of which is more valuable than of the external parts, in proportion as internal diſeaſes of this joint are more frequent than luxations, which never happen except in thoſe terrible injuries, where all the ſoft parts belonging to the joint, are entirely torn up by the roots, ſo that the limb cannot be ſaved. The chief parts to be obſerved within the joint are the fat, and Mucous Membranes, which lubricate the joint, the Ligaments or Frenulæ, which order and regulate the motions of theſe fatty maſſes and fringes., the Semi-lunar Cartilages which, like friction-wheels facilitate the motions of the joint; and Laſtly, the great Crucial Ligaments by which the joint is ſtrengthened within, the Crucial Ligaments alone being ſtronger than the whole of thoſe Ligaments which are to be ſeen on the outſide of the joint.

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FEATURE ARTICLE

Current Review: The Acquired Immunodeficiency Syndrome (AIDS)

F.A. Shepherd, M.D, F.R.C.P.(C)*, W.K. Evans, M.D., F.R.C.P.(C)*, M.J. Bazos, B.Sc., 8T5

The Acquired Immune Deficiency Syndrome (AIDS) is a recently recognized condition in Canada, and to date approximately 49 cases have been confirmed by the Laboratory Centre for Disease Control (LCDC) in Ottawa.[1] The syndrome is characterized by a defect in cell-mediated immunity and the development of *Pneumocystis carinii* pneumonia, other severe life threatening opportunistic infections or Kaposi's sarcoma. Although the etiology of this disorder is unknown, epidemiologic aspects support an infectious etiology with a mode of transmission resembling that of hepatitis-B infection. Over 2000 cases have been reported world wide with a fatality rate at two years ranging from 20-70% depending upon the associated clinical disease. Current problems including diagnosis, treatment of complicating infections and malignancies and prognosis are discussed.

Introduction

In July 1981, the Centers for Disease Control (CDC) in Atlanta, Georgia first reported the unusual occurrence of Kaposi's Sarcoma (KS), *Pneumocystis carinii* pneumonia (PcP) and other severe opportunistic infections (OOI) in previously healthy homosexual males in the United States.[2,3] In all cases there was evidence of a severe acquired cellular immunodeficiency characterized by cutaneous anergy, lymphopenia, T-lymphocyte depletion, decreased lymphocyte proliferative responses, and defective natural-killer-cell activity.[4] Since the initial reports, the number of documented cases has increased rapidly, and in September of 1983 the CDC reported a total of 2,259 cases of which 917 had died, yielding a case fatality rate of 41%. Although the majority of cases in the United States have occurred in homosexual or bisexual men (75% of cases), other population groups at high risk have been identified. These include intravenous drug abusers (13%)[5], Haitian immigrants to North America (6%)[6], hemophiliacs (less than 1%)[7], and a heterogeneous group including prostitutes, recipients of blood products[8], and infants[9], spouses or partners[10] of individuals with AIDS (less than 5%). AIDS has also been seen in a small number of patients who do not seem to fall into any of the above subgroups and are listed in Table 1.

Table 1. — Groups at Increased Risk for AIDS

- Homosexual and bisexual males
- Intravenous drug abusers
- Persons with hemophilia receiving factor VIII concentrate
- Haitians living in the United States and Haiti
- Central Africans (Zaire and Chad)
- Female and male sexual partners of patients with AIDS
- Infants and children of high risk mothers
- Prison inmates

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In Canada, the first documented case occurred in Windsor in January, 1982 and since then over 49 cases have been reported to the LCDC in Ottawa. In contrast to the American experience, 28% of Canadian cases have occurred in recent Haitian immigrants, mainly in the province of Quebec. A comparison of the Canadian and American subgroups is shown in Table 2. Twenty-nine of the Canadian cases have died yielding a case fatality rate of 59% at two years.[1]

Table 2. — Percentage Distribution of Cases, by Risk Group — Canada versus U.S.A.

Risk Group	Canada %	U.S.A. %
Homosexual/Bisexual Males	46.0	75.0
Intravenous Drug Abusers	2.0	13.0
Haitians	28.0	6.0
Hemophiliacs	4.0	1.0
Other	20.0	5.0
	100.0	100.0

Definition of AIDS

For reporting purposes, AIDS has been defined by the CDC in Atlanta as "the occurrence of a disease, at least moderately predictive of a defect in cell-mediated immunity, occurring in a person with no cause for diminished resistance to that disease".

Figure 1. CDC Surveillance Definition of AIDS

1. Biopsy proven Kaposi's sarcoma (KS) and/or biopsy or culture proven life-threatening opportunistic infection(s) (OI).
2. Previously healty persons < 60 years (KS only).
3. Excludes those patients with conditions known to cause immunosuppression (e.g. congenital immunodeficiencies, lymphoreticular malignancies, and therapy with immunosuppressive agents).

Patients must be previously healthy and under 60 years of age, and must have no pre-existing condition known to cause immunosuppression. Such diseases include biopsy proven Kaposi's sarcoma (KS), *Pneumocystis carinii* pneumonia (PcP) and other opportunistic infections (OOI) which include

pneumonia, meningitis or encephalitis due to one or more of the following: aspergillosis, cryptococcus, candidiasis, cytomegalovirus, nocardiosis, strongyloidosis, toxoplasmosis, zygomycosis or atypical mycobacteriosis (species other than tuberculosis or lepra). Gastrointestinal involvement may include esophagitis due to candidiasis, cytomegalovirus or herpes simplex virus, chronic enterocolitis (more than four weeks) due to cryptosporidiosis or unusually extensive mucocutaneous herpes simplex of more than five weeks duration. The organisms seen in life-threatening opportunistic infections in AIDS are listed in Table 3.

Table 3. — Life Threatening Opportunistic Infections in AIDS

Bacterial
- Gram-negative aerobic bacilli, including *Klebsiella pneumoniae*
- *Mycobacterium avium-intracellulare*
- *Mycobacterium tuberculosis*
- *Legionella pneumophilia*
- Nocardia

Fungal
- *Candida albicans*
- *Cryptococcus neoformans*
- *Histoplasma capsulatum*
- *Petriellidium boydii*
- *Aspergillus*

Protozoal
- *Pneumocystis carinii*
- *Entamoeba histolytica*
- *Toxoplasma gondii*
- *Cryptosporidum species*
- *Isospora belli*

Viral
- Cytomegalovirus (CMV)
- Herpes simplex virus (HSV)
- Epstein-Barr virus (EBV)
- Varicella zoster virus (VZV)
- Adenoviruses

The Clinical Spectrum of AIDS

The presenting symptoms and clinical manifestations of AIDS patients are often nonspecific, and there is no symptom complex which is diagnostic of this syndrome. At the time of diagnosis, AIDS patients may give a history of one or more of the following:

1. Periodic fevers of unknown origin, shaking chills or night sweats not accompanied by a known illness and lasting longer than several weeks.
2. Unexpected weight loss greater than 10 lbs. in less than two months.
3. Extreme and persistent fatigue or malaise.
4. Unexplained peripheral lymphadenopathy in two or more non-contiguous sites.
5. Mucocutaneous candidiasis.
6. Persistent diarrhea.

More specific presenting signs and symptoms depend on the nature of the infection or malignancy and the organ system involved. Patients with KS often have painless nodular skin lesions. This may be associated with lymphadenopathy, and if there is gastrointestinal involvement there may be a history of epigastric pain, or upper or lower gastrointestinal bleeding. PcP or pneumonia due to OOI is often preceeded by a persistent dry cough and progressive shortness of breath. Patients with gastrointestinal involvement due to atypical mycobacteria or other organisms frequently give a history of failure to respond to antibiotic therapy for more common bacterial or parasistic diseases.

Neoplasms occurring with AIDS

Several neoplasms occur in made homosexuals with AIDS and are listed in Table 4. Perhaps the most fascinating of these, is the endothelial neoplasm called Kaposi's sarcoma (KS) which is discussed separately in the following article.

Table 4. — Neoplasms occurring in male homosexuals with AIDS

- Kaposi's sarcoma
- Non-Hodgkin's lymphoma of Burkitt's type (undifferentiated monoclonal B-cell lymphoma)
- Immunoblastic sarcoma
- Cloacagenic carcinoma of rectum
- Squamous carcinoma of rectum
- Squamous carcinoma of tongue

Laboratory abnormalities in AIDS

General laboratory investigations are often unrewarding and usually are not diagnostic. Routine hematology generally shows only a lymphopenia, although this may be severe. Some patients also have thrombocytopenia which has been shown to be secondary to immune destruction associated with circulating antigen-antibody complexes.[11] Routine biochemistry is usually normal in the absence of specific organ involvement.

Immunological Studies in AIDS

All patients with AIDS have evidence of a severe defect of immune regulation. Sophisticated immunologic laboratory testing has shown abnormalities in many immunologic parameters, but unfortunately, no single test has emerged as either diagnostic or predictive of AIDS.

Humoral Immunity

Polyclonal elevation of the immunoglobulins, most frequently IgG and IgA, is often present. Humoral antibody responses are usually normal as evidenced by normal isohemagglutinin titres, and persistent serological evidence of previous exposure to cytomegalovirus, Epstein-Barr virus, and the Hepatitis B virus. Primary and secondary antibody responses to pneumococcal, influenza, diphtheria and tetanus vaccines are usually normal, although the *in vitro* response to pokeweed mitogen (PWM), a B-cell mitogen, and phytohaemagglutinin (PHA) have been found to be low in AIDS patients. Many patients have elevated circulating immune complexes, but specific antigens have not yet been isolated from these complexes. They have been implicated as a possible cause for immune thrombocytopenia through an "innocent bystander" mechanism. Weakly positive antinuclear antibodies have been found in 10 to 20% of cases.

Cell-Mediated Immunity

Leukopenia and lymphopenia are seen commonly, and atypical lymphocytes may be present in the peripheral blood film.

Two T-cell subsets control the regulation of antibody synthesis. The helper/inducer T-cell subset bears the T4 antigen

recognized by monoclonal anti-T4 antibody, whereas the suppressor/cytotoxic T-cell subset expresses a T8 antigen detected by monoclonal anti-T8 antibody. Antibody synthesis results from a delicate balance between these two subsets. T4 cells are required for B-cell differentiation into antibody producing cells and T8 cells suppress and control this differentiation.

In AIDS, there is an increase in the absolute number of T8 suppressor T-cells along with a decrease in T4 helper T-cells. A T4/T8 ratio below one is considered to be a hallmark of this syndrome, although by itself it is not diagnostic. Responsiveness of lymphocytes to the T-cell mitogens, phytohaemagglutinin and concanavalin-A are frequently reduced.

Other Immunologic Parameters

Several abnormalities of the interferon system have been found in patients with AIDS. Elevated levels of an unusual acid labile alpha interferon have been found, although this has also been reported in patients with autoimmune diseases. Natural killer cell activity, which is stimulated by interferon is often reduced in patients with AIDS. The response of 2′-5′-A synthetase response to stimulation by interferon *in vitro* may be reduced, although 2′-5′-A synthetase levels *in vivo* may be increased. Beta-2-microglobulin, a lymphocyte surface protein, and the thymic hormone alpha-1-thymosin have been found to be elevated. Finally, decreased levels of the enzyme nucleoside phosphorylase have been found, suggesting that altered T-cell function may be due to abnormal purine metabolism.

Etiology of AIDS

The common underlying factor in AIDS is a profound failure of the immune system. The cause of this severe acquired immunodeficiency is as yet unknown. Figure 2 illustrates some possible etiologic mechanisms.

Figure 2. Etiology of AIDS

Infectious	Genetic	Drugs	Autoimmune
Repeated CMV New strain of CMV New virus (e.g. HTLV)	HLA-DR5	Nitrites (Amyl or Butyl)	Sperm antibodies

The eventual outcome of AIDS, either Kaposi's sarcoma or opportunistic infection, is undoubtedly a secondary phenomenon.

Antigens on the surface of spermatozoa have been shown to induce the production of sperm antibodies in some cases of male infertility. Furthermore, certain inhalent drugs such as amyl and butyl nitrites [16] have been shown to affect immune function and particularly the cell mediated component of the immune system. Although these substances might compromise further the immune system of affected individuals, the fact that hemophiliacs and children of high risk mothers are susceptible to AIDS, provides strong evidence that drugs and autoimmune factors play an insignificant role in the origin of AIDS. Similarly, in individuals with KS, an increased frequency of the HLA-DR5 locus has been documented (63% in KS patients vs. 23% in controls)[17] suggesting a genetic predisposition towards this particular outcome of AIDS but not necessarily an initiating factor.

An infectious origin of AIDS is supported by several factors such as the clustering of cases in certain areas, the probable transmission by close sexual contact and transfusion of blood products, and the exponential increase in the number of cases.

The possibility of immunosuppression secondary to viral infection has been raised. Many of the patients have evidence of previous infection by the hepatitis-B virus, the Epstein-Barr virus and cytomegalorus.

Recently, antibodies to the human T-cell leukemia virus (HTLV) have been found in some AIDS patients, and seem to be more prevalent in healthy homosexuals than in the general population.[12] HTLV is an RNA retrovirus which infects and helps destroy the T-helper cell population. HTLV is a mutated leukemia virus which is transmitted by blood, serum or semen that may have originated in Haiti. Dr. Myron Essex, Chairman of Department of Cancer Biology at Harvard has suggested that Haitians are a high risk group and it may be that the mutation occurred there since the leukemia virus is known to exist in the Caribbean basin where Haiti is located.[12] This appealing theory is supported in that in several hundred samples of serum, many of the samples from AIDS patients have contained antibodies to HTLV virus compared with 5% of those from healthy homosexual males. However, both populations were also infected with CMV. Thus, the significance of these findings remains unclear.

Transient immunosuppression is known to follow many viral infections and abnormalities of lymphocyte function and T-cell subsets similar to those seen in the AIDS patients have also been found, and may persist for many months. Cytomegalovirus has been proposed as a possible cause for the initial immunosuppression since high antibody titres have been found in most patients, the virus can persist in semen for months at a very high titre[13], infection with the virus causes immunosuppression in humans[14], and, recently, the cytomegalovirus genome has been detected in Kaposi's sarcoma tissue[15]. If cytomegalovirus is the cause of the immunosuppression, it is difficult to explain why this syndrome appears to be new, or why the immunosuppression persists in these previously healthy individuals. It is necessary to have prolonged or repeated exposure to the causative agent, or is repeated exposure to multiple antigenic challenges a possibility?

Diagnosis of AIDS

Since many of the presenting signs and symptoms of AIDS patients are nonspecific, it is frequently difficult to arrive at a diagnosis without intensive investigation and special techniques. Any patient in one of the high risk groups for AIDS manifesting any of the signs or symptoms discussed above should undergo aggressive investigation to rule out opportunistic infection or malignant disease. It should be remembered that immune deficiency in the AIDS victim may impair the patient's ability to mount the typical immune response which might ordinarily lead to a diagnosis.

Patients presenting with skin lesions should have an immediate biopsy, and it is important to note that in AIDS patients many of the KS lesions initially may look quite benign and not have the classic purplish-red nodular features. To make the diagnosis of KS, it may be necessary to biopsy lymph nodes, or lesions in the mouth, stomach or anal-rectal areas.

Skin testing is usually unrewarding since most patients have cutaneous anergy. Despite this, it should be remembered that many of these patients will grow atypical mycobacterial organisms. Stains for acid fast bacillae should be done routinely on all biopsy specimens even in the absence of classic patholgical changes since many AIDS patients do not seem to be able to mount the typical granulomatous inflammatory reaction. Biopsy specimens must be sent for culture, and special stains should be done for parasites and fungi.

Immunologic abnormalities will provide supportive evidence, but laboratory evidence of immunodeficiency in the absence of opportunistic infection or malignant disease is not diagnositic of AIDS.

AIDS Related Complex (ARC)

The currently accepted CDC definition of AIDS encompasses only the most severe and potentially fatal manifestations of impaired cell mediated immunity. Since the first reports of AIDS, other unusual and unexplained phenomena have been described in previously healthy homosexual males; for example, Burkitt's-like-lymphoma[18], non Hodgkin's lymphoma[19] and immune thrombocytopenic purpura[11]. Cases of persistent generalized lymphadenopathy in young homosexual males have been reported[20] and some of these have progressed to meet the current CDC case definition of AIDS. Recognizing that many of the nonspecific symptoms of fever, weight loss, fatigue and generalized adenopathy may be prodromal, and that overt AIDS may represent only the "tip of the iceberg", the CDC has issued guidelines for the diagnosis of a "preAIDS" syndrome called the AIDS Related Complex (ARC). These guidelines are outlined in Table 5.

Table 5. — The AIDS Related Complex (ARC)

I. 2 or more **clinical signs/symptoms** lasting 3 months,

PLUS

II. 2 or more **laboratory abnormalities** lasting 3 months,

occuring in a patient who, (A) has no underlying infectious cause for the above, and (B) is in a cohort at increased risk for developing overt AIDS.

Clinical Signs/Symptoms include:

1) Fever: ⩾ 39°C, intermittent or continuous
2) Weight loss: unexplained 10% or 15 lbs.
3) Lymphadenopathy in 2 continuous areas
4) Diarrhea
5) Fatigue
6) Night sweats

all at least of 3 months duration.

Laboratory Abnormalities include:

1) Leukopenia, thrombocytopenia, absolute lymphopenia or anemia
2) Depressed T4/T8
3) Decreased No. T helper
4) Decreased blastogenesis (PWM and PHA)
5) Increased serum globulins
6) Cutaneous anergy.

It is not definitely clear at this time what proportion of patients with ARC will proceed to fulminating AIDS. Furthermore, no specific treatment is available for this syndrome. Patients who fall into this group should be evaluated thoroughly, followed closely and treated promptly for opportunistic infections or KS should they occur.

The Treatment of AIDS

Specific treatment of course will be directed by the particular neoplasm or opportunistic infection which is present. Unfortunately, despite appropriate antibiotic treatment and the use of a variety of antineoplastic therapies, the mortality rate remains extremely high. Three years survival for AIDS patients is less than 15%.

Attempts have been made at immune reconstitution, using interferon[21], but even though regression has been in some patients with Kaposi's sarcoma, immune function rarely returns to normal. Thymic hormone extract has been tried in the "gay lymphadenopathy syndrome" without significant benefit[22]. Trials with purified human interleukin-2 are underway currently, but results are not yet available.

It is unlikely that adequate treatment for this syndrome will become available until a cause for the immunodeficiency can be determined. It must be hoped that out of this bizarre disorder will arise a clearer definition and understanding of the relationship between the human immune system, viral infection and oncogenesis.□

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References

1. Personal Communication Dr. Gordon Jessamine, Laboratory Centre for Disease Control, Ottawa, Ontario, Canada.
2. Kaposi's sarcoma and pneumocystis pneumonia among homosexual men — New York City and California. *Morbidity and Mortality Weekly Report 30*:305-308, 1981.
3. Followup on Kaposi's sarcoma and pneumocystis pneumonia. *M.M.W.R. 30*:409-410, 1981.
4. Gotlieb M.S., Schroffr, Schanker H.M. *et al.*: *Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men, evidence of a new acquired cellular immunodeficiency. *N. Engl. J. Med. 305*:1425-1431, 1981.
5. Masur H., Michelis M.A., *et al.*: An Outbreak of Community-Acquired *Pneumocystis Carinii* Pneumonia. Initial Manifestations of Cellular Immune Dysfunction. *N. Engl. J. Med. 305*:1431-1438, 1981.
6. Hensley G.T., Moskowitz L.B., *et al.*: Opportunistic Infections and Kaposi's Sarcoma among Haitians in the United States. *M.M.W.R. 31*:353-354, 360-361, 1982.
7. Ehrenkranz N.J., Rubini J., *et al.*: *Pneumocystis carinii* Pneumonia among Persons with Hemophilia A. *M.M.W.R. 31*:365-367, 1982.
8. Ammann A., Cowan M., *et al.*: Possible Transfusion-Associated Acquired Immune Deficiency Syndrome (AIDS) — California. *M.M.W.R. 31*:652-654, 1982.

9. Joneas J.H., Delage G., and Chad Z.: Acquired (or Congenital) Immune Deficiency Syndromes (AIDS) in Infants Born of Haitian Mothers — Quebec. *C.D.W.R. 9-4*:13-14, 1983.

10. Harris C., Butkus Small C., *et al.*: Immunodeficiency among Female Sexual Partners of Males with Acquired Immune Deficiency Syndrome (AIDS) — New York. *M.M.W.R. 31*:697-698, 1983.

11. Morris L., Distenfeld A., *et al.*: Autoimmune thrombocytopenic purpura in homosexual men. *Ann. Int. Med. 96* (Pt. 1):714-717, 1982.

12. Essex M., McLane M.F., *et al.*: Antibodies to cell membrane antigens associated with human T-cell leukemia virus in patients with AIDS. *Science 220*:859-862, 1983.

13. Lang D.J., Kummer J.F., Hartley D.P.: Cytomegalovirus in semen: persistence and demonstration in extracellular fluids. *N. Engl. J. Med. 291*:121-123, 1974.

14. Carney W.P., Rubin P.H., Hoffman R.A., *et al.*: Analysis of T lymphocyte subsets in cytomegalovirus monocucleosis. *J. Immunol. 126*:2114-2116, 1981.

15. Boldogh I., Beth E., Huanges, *et al.*: Kaposi's sarcoma. IX. Detection of CMV DNA, CMV RNA and CMNA in tumor biopsies. *Inter. J. Cancer 28*:469-474, 1981.

16. Geodert J.J., Wallen W.C. *et al.*: Amyl Nitrite May Alter Lymphocytes in Homosexual Men. *Lancet*:412-415, 1982.

17. Firedman-Kein A.E., Laubenstein L.J., *et al.*: Disseminated Kaposi's sarcoma in homosexual men. *Ann. Int. Med. 96* (Pt. 1):700-704, 1982.

18. Fiegler J.L., Drew W.L., Miner R.C., *et al.*: Diffuse, Undifferentiated Non-Hodgkin's Lymphoma among Homosexual Males — United States. *M.M.W.R. 31*:277-279, 1982.

19. Ziegler J.L., Wagner G., *et al.*: Diffuse, Undifferentiated Non-Hodgkin's Lymphoma among Homosexual Males — United States. *M.M.W.R. 31*:277-279, 1982.

20. Mildran D., Mathur U., *et al.*: Persistent, Generalized Lymphadenopathy among Homosexual Males. *M.M.W.R. 31*:249-251, 1982.

21. Krown S.E., Real F.X., Cunningham-Rundles S., *et al.*:Preliminary observations on the effect of recumbinant leukocyte A interferon in homosexual men with Kaposi's sarcoma. *N. Engl. J. Med. 308*:1071-1083, 1983.

22. Oswald G.A., Theodossi A., Guzzard B.G., *et al.*:Attempted immune stimulation in the "gay compromised syndrome". *Br. Med. J. 285*:1082, 1982.

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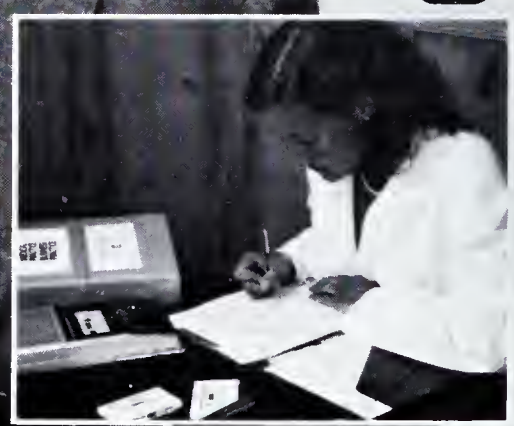

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ONCOLOGY

Kaposi's Sarcoma: "Multiple Idiopathic Pigmented Skin Sarcoma"

T. Tarshis, 8T5, M.J. Bazos, B.Sc., 8T5, W.K. Evans, M.D., F.R.C.P.(C)*, F.A. Shepherd, M.D., F.R.C.P. (C)*

Kaposi's sarcoma (KS) has recently become an intriguing clinical mystery linking immunology, oncology, virology, and lifestyle. In the past two years, the outbreak of KS in patients with the Acquired Immune Deficiency Syndrome (AIDS) has focused attention on the relationship between neoplasia and competence of the immune system. It is hoped that research into this disease process will provide new insights into the pathogenesis and treatment, not only of KS, but also of other malignancies. This paper outlines the clinical and pathological features of KS beginning with a case report. For a discussion of the etiology and the immunological abnormalities of AIDS-related KS, the reader is referred to the preceding paper.

Case Report

A 37 year old male homosexual presented to Toronto General Hospital with a four week history of non-tender, non-pruritic purplish skin lesions involving the anterior chest wall, the medial aspect of the left thigh and the dorsum of the forearm. He denied any fatigue, weight loss, fever, chills or night sweats, diarrhea or melena, cough or shortness of breath. The patient gave no history of hepatitis or blood transfusion. He had been a practising homosexual for eight years engaging in both oral and anal sex, and had had over one hundred partners including sexual contacts with New York homosexuals in the last year. He smoked marijuana daily and used amyl nitrite regularly. He denied intravenous drug use.

On physical examination the only positive findings were confined to the skin where several small, slightly purplish nodules measuring less than 1 cm in diameter were noted on the chest, arms and legs.

Fig. 1

Fig. 2

Fig. 1 and 2 These gross and magnified views of the left lower leg show elliptical purple skin nodules which measures 1 × 0.6 cm. There is a violateous central elevated circumscribed nodule which measures 0.5 cm in the largest diameter.

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There was no lymphadenopathy and no hepatosplenomegaly. Rectal examination was normal although sigmoidoscopy revealed four small nodular red lesions at 10 cm from the anal orifice.

Course and Investigations in Hospital

The hemoglobin was 151 g/L, leucocyte, 6.5 × 10⁹/L. Differential: 73% neutrophils, 20% lymphocytes, 1% monocytes, 6% eosinophils and the platelet count was 165 × 10⁹/L. All biochemistry was normal, as was a routine urinalysis. Stool was negative for Salmonella, Shigella and Campylobacter. The VDRL was negative. A complement fixation test for CMV yielded a titre greater than 1/64; the patient's serum was negative for hepatitis-B surface antigen but positive for antibody to Epstein Barr virus (VCA 1:320; EA 1:20). The chest X-ray was normal.

Skin biopsies were obtained from the left lower arm, left upper arm and left lower leg and a diagnosis of Kaposi's sarcoma was made.

Fig. 3 and 4 Light microscopy preparation from skin biopsy. There are an increased number of spindle cells arranged in interweaving fascicles and a patchy mononuclear cell infiltrate containing plasma cells. Mitotic figures are absent. The cleft-like vascular spaces are associated with extravasated red blood cells and hemosiderin deposition.

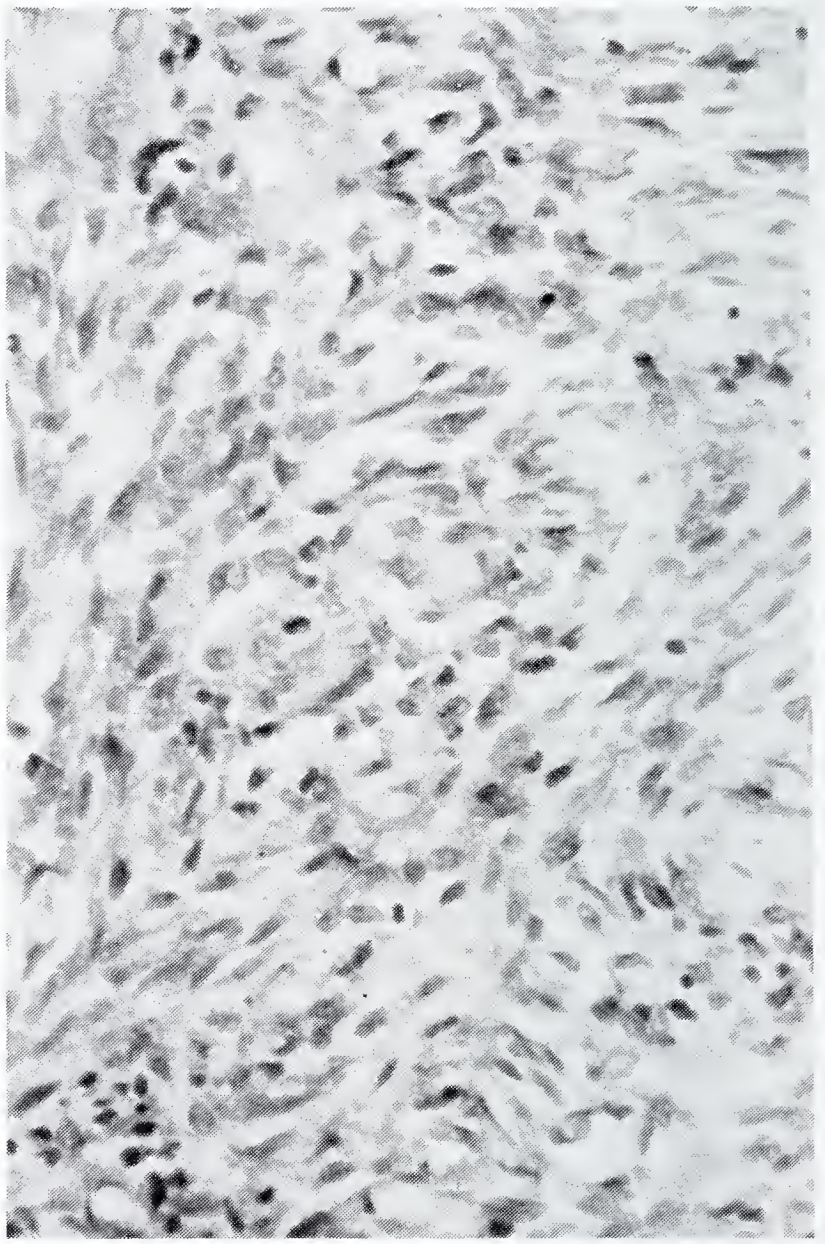

Fig .4

Rectal lesions were also biopsied and reported as consistent with KS as shown in figure 5.

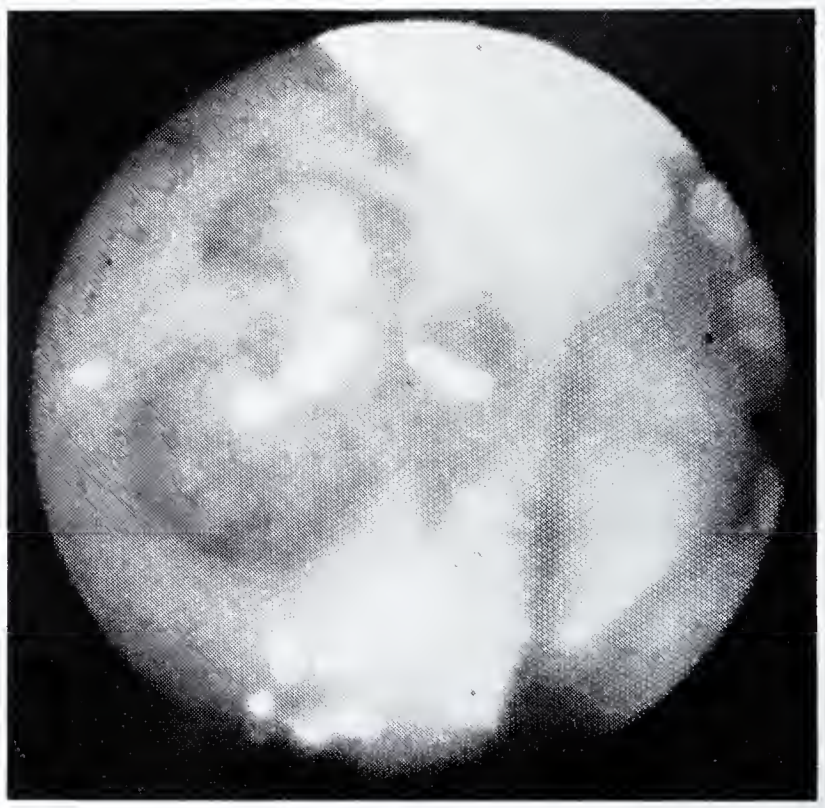

Fig. 5 Sigmoidoscopy of rectal lesions at 8 cm inside the anal verge. Four nodules are shown, ranging in size from 1/2 cm to 1 cm. The nodules are red peripherally with central bluish-white depressions.

Immunologic Investigation

Skin tests were positive for Candida and negative for mumps and TB. There was an inversion of the T4/T8 ratio due to an increase in the relative percentage of T suppressor cells and a decrease of T helper cells (Table 1). IgG and IgM were normal, but IgA was increased at 6.4 g/L (Table 2).

Table 1. Cell Surface Markers

T-Lymphocytes	Patient	Normal Range
E Rosettes	64	55 - 73
T3	51	55 - 73
T4	18	36 - 58
T8	36	20 - 28
T4/T8	0.5	1.6 - 2.5
B1 Lymphocytes	8	6 - 20

Table 2. Serum Protein Immunoelectrophoresis by Laser-Nephelometry Method

Immuno-electrophoresis	Patient Quantitations (g/L)	Normal Range
IgG	14.1	8 - 18
IgA	6.4	0.9 - 4.5
IgM	1.5	0.6 - 2.8

The patient was started on a chemotherapy-immunotherapy treatment program consisting of actinomycin D 1.0 mg/m^2, vinblastine 6 mg/m^2 and bleomycin 15 units/m^2 intravenously on day 1 and day 8. On day 15, interferon 20 × 10^6 units was started cutaneously three times a week for two weeks. The treatment cycle was repeated at 28 day intervals.

The patient has completed three treatment cycles and has tolerated the drugs well with minimal toxicity. He has had no new symptoms and the cutaneous lesions have all flattened leaving only minor skin discolouration. In addition, no new lesions have appeared and no lymphadenopathy or organomegaly has developed. The patient remains on treatment, and is doing well.

Epidemiology and Clinical Manifestations

In 1872, Dr. M. Kaposi[1] described a condition of patients with "multiple idiopathic pigmented sarcoma of the skin". This tumour, now named Kaposi's sarcoma, is a malignant condition that affects the skin, lymphoid tissue, and internal organs.

It is a rare tumour and represents only about 0.02% of all malignancies in North America[2]. Until the beginning of this decade, almost all cases were restricted to certain ethnic groups, specific geographic regions or transplant patients on chronic immunosuppressive therapy. However, in the last two years, an outbreak of KS has been seen in North America as part of the Acquired Immune Deficiency Syndrome (AIDS)[3,4].

The classical variety of KS affects elderly Ashkenazi Jews and males from the Mediterranean area. This form of KS is generally an indolent disease process confined to the skin of the lower extremities.[5] Initially, the lesions resemble capillary hemangiomas, chronic inflammation or stasis purpura. Individual lesions may regress as others progress and ulcerate. In time, lymphedema develops and regional nontender lymphadenopathy may appear.

In Africa, KS occurs in the "lymphoma belt" of central and western Africa and manifests as a clinically aggressive disease commonly associated with lymphoid and visceral involvement.[6] In fact, in this variant of KS, lymphatic and visceral involvement may precede the development of skin lesions.

KS is the most common form of cancer in AIDS victims. Amongst homosexuals with AIDS, the average age at presentation with KS is 35 years. The age-specific risk of developing KS for homosexuals living in large cities is approximately 100 times that of non-homosexuals.[7] The AIDS-associated KS variant bears a strong resemblance in its clinical manifestations to that of the aggressive African form of KS. The most common presenting complaints are weight loss, fatigue, night sweats, fever, chills, lymphadenopathy and abdominal tenderness. In over 50% of cases, cutaneous lesions are the initial sign of disease. Lesions may appear anywhere on the skin and/or mucous membranes, and often are rapidly progressive. Internal organs are affected commonly and lymphadenopathy is often present. KS may involve any level of the GI tract and manifests itself as nausea, vomiting, abdominal pain, diarrhea or melena. Occasionally the lesions produce obstruction of the small or large intestine or cause malabsorption. Respiratory tract involvement may result in cough, hemoptysis or dyspnea. Other sites of involvement include the pleura, pericardium, heart, adrenals, liver, bone marrow and central nervous system.

The presenting symptoms and clinical course of KS in transplant recipients on immunosuppressive therapy often parallel those seen in patients with AIDS. A fulminant course may warrant withdrawal of the immunosuppressants. Regression of KS will then occur in approximately 50% of patients although often at the expense of rejection of the transplanted organ.[8]

Pathology

The gross appearance of the cutaneous lesions varies greatly. Their colour ranges from pink to red to violet and brown depending on the vascularity of the tumours, the extent of extravasation of red blood cells and hemosiderin deposition. The lesions may be patch-like, nodular or plaque-like in configuration and their size may extend from the minute to 6-8 cm in diameter. Although there is controversy regarding the cell of origin of KS, a positive stain for factor VIII supports the idea that this neoplasm is of endothelial origin.[9] Microscopically, one sees an increased number of small blood vessels lined with cells resembling endothelial cells along with a proliferation of spindle shaped cells.[10] Inflammatory cells with hemosiderin-laden macrophages are often seen. The lesions have been classified as granuolmatous, angiogranulomatous, angiomatous and sarcomaous.[9]

Granulomatous lesions are composed of fibrous tissue, chronic inflammatory cells and scantily distributed dilated

capillaries. The stroma may be edematous. Areas of focal hemorrhage may also be seen.

Angiomatous lesions contain more capillaries in a tangled arrangement, lined by a layer of endothelial-type cells with hyperchromatic vesicular nuclei. Some regions of the capillaries are encircled with pericyte-like spindle-shaped cells. The stroma contains collagen fibers and some fibroblast-like spindle cells.

The sarcomatous lesion shows bundles of spindle-shaped cells, among which are slit-like spaces containing red blood cells.

The KS lesions progress with hypercellularity but mitotic figures are uncommon. From the pathologist's point of view, the differential diagnosis includes stasis dermatitis, other vascular tumours, fibrosarcomas and neural tumours.

Prognosis

The prognosis of a patient with KS is determined by the variant of KS and the extent of involvement at presentation. The indolent form of KS affecting Jews and males from the Mediterranean basin area is very rarely a cause of mortality. Only 10 - 20 per cent of the deaths are due to the sarcoma. This form of KS has a median survival of 8 to 13 years from diagnosis.[11]

The African form of KS is much more aggressive and usually runs a fulminant course. Death almost always occurs within two years of presentation.[12]

KS occurring in the immunosuppressed individual is often resistant to treatment unless regression occurs with cessation of immunosuppressants. Death in these cases often results from gastrointestinal hemorrhage or infection. In the patient with AIDS and KS, the 20 month survival may be as low as 50 per cent.

Treatment

A variety of treatment modalities have been attempted in the management of KS.

Radiotherapy (local and extended field radiation) is the treatment of choice in the indolent form of KS due to the extreme sensitivity of this form of the tumour to radiation. Localized lesions may also be treated with excision, electrodessication, curretage or by electrocoagulation.

Chemotherapy has been useful in the treatment of the African form of KS. Actinomycin D has shown significant antitumour activity as a single agent, and combinations including this agent with vincristine and dacarbazine have been particularly effective, yielding complete responses in the majority of cases (30/32 complete response in one series). Bleomycin and dacarbazine have also shown activity against this variant of KS.[13]

The experience with cytotoxic chemotherapy against the epidemic form of KS in AIDS is recent but rapidly accumulating. Both vinblastine and the epipodophyllotoxin VP-16, have shown significant activity against limited, indolent disease.[14,15] For advanced or rapidly progressive diseases, the combination of adriamycin 40 mg/m^2 day 1, bleomycin 15 mg/m^2 day 1 and 15 and vinblastine 6 mg/m^2 day 1 has been used in several centres.[14,15] Laubenstein has reported that 86% of patients respond to this form of treatment although only the minority achieve a complete response (18%). In addition, the median response duration is approximately 7 months and no patient has had a response longer than 12 months. The median duration of survival has been 14 months.[14]

The underlying immunodeficiency in these patients persists and episodes of opportunistic infection often complicate therapy. These observations highlight the need to apply treatment that might correct the underlying immunodeficiency syndrome.

Interferon has been demonstrated to have stimulatory activity on human natural killer cells, cytotoxic T cells and macrophages. Its side effects include fatigue, headaches, chills, myalgia, change in taste and nausea; however, a potential major advantage is the fact that it lacks the immunosuppressive effects of cytotoxic chemotherapy.

Historically, interferon was recognized and characterized as a cell-derived protein with the capacity to protect eukaryotic cells against viral infection; this property is still utilized for the expression of interferon potency. Interferon is not directly toxic to viruses, but instead triggers an intracellular response which prevents infection by interfering with viral replication. Thus, the interferon antiviral response to the same virus may vary among the responsivity of the host to interferon. This level of cellular resistance is regulated in part by surface interferon receptors encoded on chromosome 21 in humans. A transient interaction of interferon and its receptor is sufficient to initiate the sequence of metabolic events (RNA and protein synthesis) producing the antiviral state. This condition can be maintained indefinitely, but only with the continued presence of interferon.

Preliminary clinical trials have shown that both natural and recombinant-DNA-produced human interferon are occasionally capable of inhibiting the growth of some tumours including those in which a viral etiology is implicated.[16,17] A recent report using highly purified human alpha-interferon produced by recombinant-DNA technology in 12 patients with KS, described five major objective responses and three minor responses.[18]

Although it is premature to make firm recommendations, it may be worthwhile to investigate the effect of combining the effect of combining biological response modifiers such as interferon with other cytoreductive agents in the treatment of Kaposi's sarcoma. This is currently the strategy for the treatment of AIDS-related KS at the University of Toronto.□

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References

1. Harwood, A.R., Osaba D., Hofstadin, S.L. *et al.*: Kaposi's Sarcoma in Recipients of Renal Transplants. *Am. J. Med. 67*:759-765, 1979.

2. Kaposi's sarcoma and pneumocystis pneumonia among homosexual men — New York and California, *Mortality and Morbidity Weekly Report 30*:305-308, 1981.

3. Followup on Kaposi's sarcoma and pneumocystis pneumonia. *M.M.W.R. 30*:409-410, 1981.

4. Gotlieb M.S., Schroffr, Schanker H.M., *et al.: Pneumocystis carinii* pneumonia and mucosal candidiasis in previously healthy homosexual men, evidence of a new acquired cellular immunodeficiency. *N. Engl. J. Med. 305*:1425-1431, 1981.

5. Masur H., Michelis M.A., *et al.*: An Outbreak of Community-Acquired *Pneumocystis carinii* Pneumonia. Initial Manifestations of Cellular Immune Dysfunction. *N. Engl. J. Med. 305*:1431-1438, 1981.

6. Hensley G.T., Moskowitz L.B. *et al.*: Opportunistic Infections and Kaposi's Sarcoma among Haitians in the United States. *M.M.W.R. 31*:353-354, 360-361, 1982.

7. Center for Disease Control Task Force on Kaposi's Sarcoma and Opportunistic Infections: Special Report in *N. Engl. J. Med.*, Jan. 28, 1982.

8. Ehrenkranz N.J., Rubini J. *et al.: Pneumocystis carinii* Pneumonia among Persons with Hemophilia A. *M.M.W.R 31*:365-367, 1982.

9. Tange, Tsuyoshi: Kaposi's Sarcoma — Case Report and Review of Japanese Cases. *Acta Path. Jap. 29(2)*:319-332, 1979.

10. Robbins, S.L., Cotran, R.S.: Pathologic Basis of Disease, 2nd ed. W.B. Saunders Company. Toronto, 639, 1930, 1979.

11. Gerstuft, J. *et al.*:Severe Acquired Immunodeficiency in European Homosexual Men. *Brit. Med. J. 285*:July, 1982.

12. Friedman-Kien, Alvion E.: Disseminated Kaposi's Sarcoma Syndrome, *J. Am. Acad. Dermatol. 5*:4: October, 1981.

13. De Wys Wo, Curran J., Henle W., Johnson G.: Workshop on Kaposi's Sarcoma: Meeting Report. *Cancer Treat. Rep. 66*:1387-1390, 1982.

14. Laubenstein L.J., Krigel R.L., Hymes K.B., Muggia F.M.: Treatment of Epidemic Kaposi's Sarcoma with VP-16-213 and a combination of doxorubicin, bleomycin and vinblastine. *Proc. Am. Soc. Clin. Oncol.* Abst. C-892, 1983.

15. Lewis B., Abrams D., Ziegler J., Conant M., Gie G., Siverberg I., Volberding P.: Single Agent or Combination Chemotherapy of Kaposi's Sarcoma in Acquired Immune Deficiency Syndrome. *Proc. Am. Soc. Clin. Oncol.*, 1983.

16. Treuner J., Neithammer D., Daynelker G., Hagmann R., Neef V., Hofschneider P.: Successful treatment of nasopharyngeal carcinoma with interferon. *Lancet 1*:817-818, 1980.

17. Hagbind S., Lundquist P.G., Cantill K., Strander H.: Interferon therapy in juvenile laryngeal papillomatosis. *Arch. Otolaryng. 107*:327-332, 1981.

18. Krwon S.E., Real F.X., Cunningham-Rundles S., Myskowski P.L., Koziner B., Fein S., Mittelman A., Oeitgen H.F., Safar B.: Preliminary observations on the effect of recombinant leukocyte A interferon in homosexual men with Kaposi's sarcoma. *N. Engl. J. Med. 308*:1071-1076, 1983.

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ORTHOPEDICS

Displaced Subcapital Fractures of the Neck of the Femur Treated by Richard Screw Plate Fixation

J.M. Allen, 8T5

A retrospective study was carried out on 102 patients with 104 subcapital fractures of the neck of the femur, treated at Sunnybrook Medical Centre, between 1974 and 1980. All fractures were treated by closed reduction and internal fixation with a compression screw-plate system. It was found that 63% of patients surviving one year had clinically good results, while 20% had unsatisfactory results. The one year mortality was 17%. The results appeared to vary with the age of the patient. The present series suggests that the Garden classification of subcapital hip fractures does not dictate the fate either of the head of the femur or the patient.

Subcapital fractures of the neck of the femur constitute a serious problem for the aging population. There is a high incidence of both mortality and morbidity following these fractures and, while many treatment methods have evolved over the years, Dickson's description of the 'unsolved fracture'[3] is unfortunately still applicable.

The aims of surgical tratment of the displaced fracture of the femoral neck are:

1. To reduce the morbidity and mortality following injury. The one year mortality has been found to range from 27%[9] to 36%[6], and is affected by advanced age, male sex, cerebral dysfunction[9], poor physical state prior to fracture reduction, and delay in reduction of over three days[1]. This increased mortality following surgery usually continues until the sixth month after operation; deaths after this time period are usually unrelated to the original injury.[7]
2. To avoid a second operation in an elderly patient. Due to the failures encountered in the treatment of subcapital hip fractures, prosthetic replacement by total hip replacement or hemi-arthroplasty has been advocated by some[2,10]. However, it would seem true that 'the best place for a viable femoral head is on the femur', and the best place for a prosthesis is on the operating room shelf.
3. To return the patient rapidly to the preinjury social and ambulatory status. Miller[9] found that only 50% of patients surviving hip fractures resume their previous ambulatory status, while Thomas and Stevens[11] found that 25% of survivors had become more dependent. The inactivity following hip fractures can itself lead to depression and/or cause the patient to stop walking entirely.
4. To minimize the cost of the health service. As the average age for patients suffering subcapital hip fractures has been reported as 75.6 years and 69.4 years for females and males respectively[1], the high mobidity following these fractures may present serious social problems both for the patients, their families and the social service agencies that may be required to provide for the increasingly dependent aging individual.

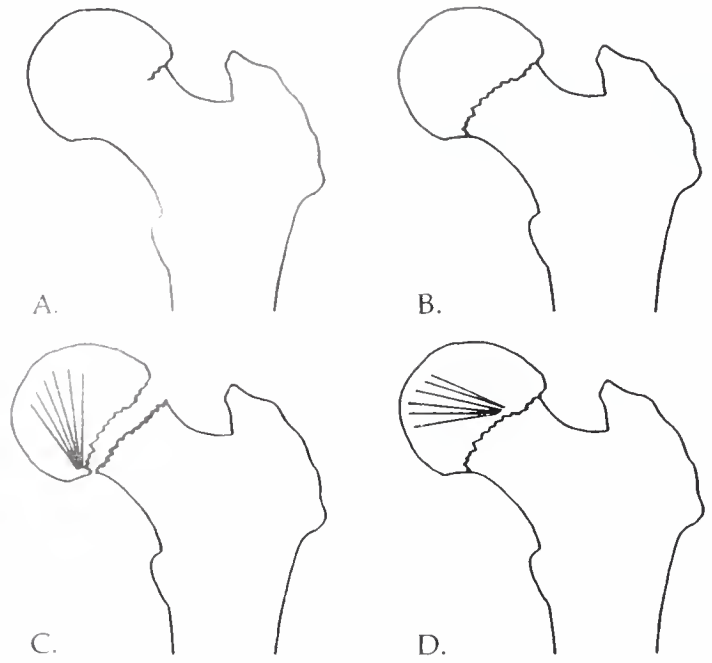
Unfortunately, these aims to date have not been met and the search has continued for an internal fixation device which would maintain the reduction and alignment obtained at surgery while allowing for bone healing. Since the late nineteenth century, when the first nail was used to stabilize a hip fracture[12], a variety of nail and plate combinations have been employed. The nail should allow for some lateral and distal sliding thus facilitating bone healing; if no sliding takes place, the nail may penetrate the hip joint. However, if too much sliding occurs, the fracture may again become unstable resulting in loss of reduction of the fracture. The nail screws were introduced and later a plate was added for increased stability of the fracture site. Finally, single nail-plate systems were employed to avoid the stress weak point at the nail-plate junction which had occasionally led to breakage of the plate. Lastly, a sliding compression screw was added permitting alignment and fixation of the fracture fragments. There are now several devices available that consist of a compression lag screw with a keyed barrel preventing rotation: the entire device theoretically allowing collapse of the fracture while combining both strength and stability. Should internal fixation be desired for treatment of a subcapital hip fracture, this method is now the device of choice.

Unlike other fractures, the alignment and reduction of subcapital hip fractures obtained at surgery and ideally maintained by the fixation device, must be virtually perfect in order for union to occur. This, in turn, is dependent upon the degree of displacement occurring at the original injury. In 1971, Garden [5,8] proposed a classification system with prognostic implications, based on the degree of displacement of the fragments as indicated by trabecular alignment in the femoral head and acetabulum. This system is elaborated in Table 1 and Fig. 1.

Table 1.
Garden Classification of Subcapital Hip Fractures

Stage	Description
I	Incomplete fracture, commonly known as "impacted".
II	Complete fracture without displacement.
III	Complete fracture with partial displacement.
IV	Complete fracture with full displacement.

Fig. 1 Garden's fractures; A, Stage I; B, Stage II; C, Stage IV; D, Stage III



Garden emphasized that the degree of alignment of the reduced fracture determined the clinical outcome, particularly with reference to the development of fracture union and avascular necrosis. For example, union rates for fractures of Garden types I and II have been reported to be as high as 100%, whereas displaced types III and IV have rates of 93% and 54% respectively[1]. Garden[5,8] attributed the occurrence of avascular necrosis to the disparity in alignment of a poorly reduced fracture and suggested that the optimal outcome would result from realignment within the range of 160° to 180° as indicated by both anterior-posterior and lateral radiographs. It is suggested that Garden's classification and alignment index may provide a reliable indication of the fate of both the fracture and femoral head.

This retrospective study examined the fate of 104 subcapital hip fractures (Garden types III and IV) treated at Sunnybrook Medical Centre between 1974 and 1980. All were treated by closed reduction and internal fixation with the Richards' Compression Screw and Plate System. Mortality at both six months and one year were noted as were the complications of deep infections, avascular necrosis and mechanical failures. Both radiographic and clinical results were considered along with a minimum 18 month follow up.

Methods

The records and radiographs of all patients admitted to Sunnybrook Medical Centre between 1974 and 1980 with subcapital hip fractures (Garden types III and IV) were obtained. Attempts were made to locate these patients and obtain either a valid 18 month follow up at Sunnybrook Medical Centre with a radiograph and report of ambulatory and pain status, or a telephone report of the same, accompanied by a recent radiograph. If the patient had expired, the cause of death and clinical status with respect to the hip fracture prior to death were obtained. Age, Garden classification index, and presence of hip disease were determined prior to surgery while reduction index and pin placement were determined following surgery. At follow up, the presence of avascular necrosis, with or without collapse of the head, maintenance of reduction, and fracture union were considered.

Results

Between the years 1974 to 1980, 112 displaced subcapital hip fractures were treated at Sunnybrook Medical Centre. Of these, sufficient information existed on 102 (104 fractures) patients to make them available for review. Ten percent were lost to follow up. There were 72 females and 32 males with average ages of 74.2 and 78.5 years respectively. Overall, the average age was 77.2 years. The proportion of women to men was 2.2:1.

Table 2. — Complications Following Subcapital Hip Fractures of Garden Types III and IV, Treated by Internal Fixation

	Mortality	Failures	Avascular Necrosis	Deep Infections
6 months	10/102 (10)*	15/94 (16)	0	3/104 (3)
1 year	17/102 (17)	2/87 (2)	18/70 (26)	

*Percentages given in brackets

Mortality was considered at both six months and one year post fixation. Early failures were defined as failures of fixation occurring within six months and included protrusion of the screw, separation of the fracture, and rotation of the fracture fragments. Late failures occurred after six months. After excluding the patients who had died at one year, there were 87 fractures under consideration. Of these, 70 healed. Since avascular necrosis can only be considered in a healed fracture, the number of fractures developing this complication was 18/70 (26%).

Table 3. — Clinical Result of Subcapital Hip Fractures (Garden Types III and IV), Treated by Internal Fixation

Result	Number	Percentage
Good	55/87	(63)
C	11/87	(13)
Poor	4/87	(5)

"Good" results were defined as "minimal pain, walks 100 meters unaided with one cane and performs household duties".[11]

"C" results were defined as "good results with respect to the fate of the hip but with a clinical progress impeded by such complications as advanced age or other disease process leading to nonambulator status, e.g., hemiplegia".

"Poor" results were defined as "nonambulatory status due to fracture associated complications".

No significant difference was found between the results following a type III or type IV fracture. There were no sex or age differences found between the two types of fractures except in the age group 71-80 in women, where there was a threefold increase in type IV fractures. This age difference was also found in the age group 81-90 in men.

Discussion

While other series have found a 4:1 ratio of women to men, the present series found a 2.2:1 ratio, which is a significant difference ($p \leqslant 0.05$).

Although the Garden classification has correlated with the fate of the femoral head, fracture healing and clinical outcome in earlier series[8], this was not found in the present study. Neither quality of reduction nor poor screw placement could be correlated with the results or complications. For example, while there was radiographic evidence of 15 poor reductions, only three failed. The development of avascular necrosis did not correlate with surgical technique as suggested by Garden [5,8]. Interestingly, in the present series, while 26% of the healed fractures did develop avascular necrosis, only one quarter of these required a second operative procedure for disabling symptoms. Generally it was found that patient outcome could not be predicted from radiographs, for while some patients had a poor prognosis from radiographic evidence they nevertheless went on to a good clinical result. It was also true that patients did poorly following fractures that had appeared to be perfectly reduced and stabilized. The Garden index[5,8] obtained by measuring the angles created by the alignment of trabeculae in the femoral head with those in the acetabulum could not be accurately estimated in the present series due to the variability of both the radiographs and trabeculae themselves. Therefore reduction quality was assessed radiographically on the basis of restoration of Shenton's line, on the antero-posterion view and alignment of the fracture on the lateral view.

It was found that 63% of patients treated by internal fixation with a compression screw-plate system obtained good results while a good result was obtained in 13% but was obscured by other disease processes. If one combines the poor results with the failures, it is found that 20% of patients obtained unsatisfactory results.

In the present series, it was found that the number of poor results, and especially C results, increased with the patient's age. This has been found in other series and has encouraged other authors to adopt an alternate surgical procedure for patients with displaced hip fractures who are older than 84 years of age. This review also suggests that an alternative procedure be considered for more patients over the age of 80. Internal fixation is not advocated in patients nonambulatory prior to injury nor in very elderly senile patients who are nonambulatory[4].

Unfortunately, despite the theoretical advantage of the compression screw-plate system, a small number of patients will not be spared a second operative procedure. The present series found that the majority of patients surviving one year will obtain a good result with the internal fixation device investigated.□

Acknowledgements

I would like to thank the orthopaedic surgeons at Sunnybrook Medical Centre, Toronto, who allowed me to review their patients, and especially Dr. Gordon Hunter who helped with this review.

References

1. Barnes, R., Brown, J.T., Garden, R.S., Nicoll, E.A.: Subcapital Fractures of the Femur. *J. Bone Joint Surg.* 58B(2), 1976.
2. Coates, R.L. and Armour, P.: Treatment of Subcapital Femoral Fractures by Primary Total Hip Replacement. *Injury 11*:132, 1980.
3. Dickson, J.A.: The Unsolved Fracture. *Journal of Bone Joint Surg.* 35A, 1953.
4. Dorr, L.D.: Treatment of Hip Fractures in Elderly and Senile Patients. *Orthopedic Clinics of North America 12*:1, 1981.
5. Garden, R.S.: Malreduction and Avascular Necrosis in Subcapital Fractures of the Femur. *J. Bone Joint Surg.* 53B(2), 1971.
6. Gordon, P.C.: The Probability of Death Following a Fracture of the Hip. *C.M.A.J.* 105, 1971.
7. Hunter, G.A.: A Further Comparison of the Use of Internal Fixation and Prosthetic Replacement for Fresh Fractures of the Neck of the Femur. *Br. J. Surg.* 61, 1974.
8. London, P.S.: Classification of Fractures of the Neck of the Femur and the Technique of Reduction. *The Hip Society*, Proceedings of the 5th Open Scientific Meeting of the Hip Society, 1977, The C.V. Mosby Company, St. Louis, Toronto, London.
9. Miller, C.W.: Survival and Ambulation Following Hip Fracture. *J. Bone Joint Surg.* 60A(7), 1978.
10. Sim, F.H. and Stauffer, R.N.: Management of Hip Fractures By Total Hip Arthroplasty. *Clin. Orthop. 152*:191, 1980.
11. Thomas, T.G. and Stevens, R.S.: Social Effects of Fractures of the Neck of the Femur.*Br. Med. J.* 3, 1974.
12. Treharne, R.W.: The Compression Hip Screw. *Orthopaedic Review 11*:1, 1982.

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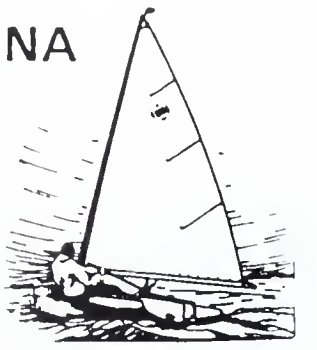

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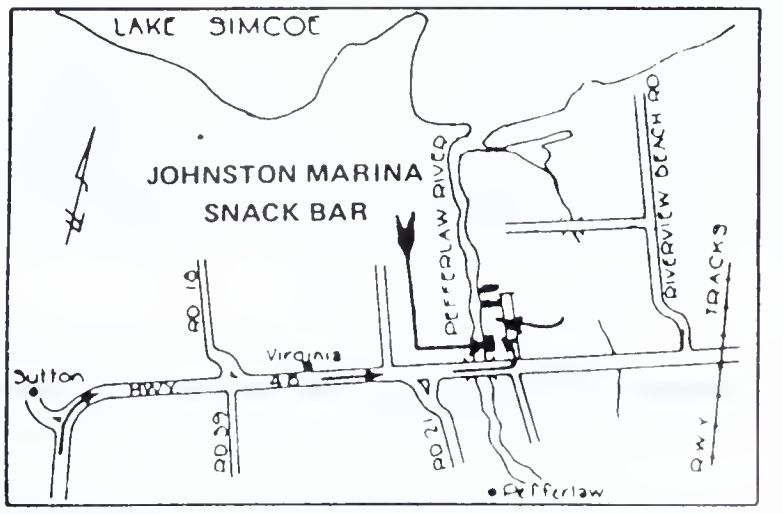

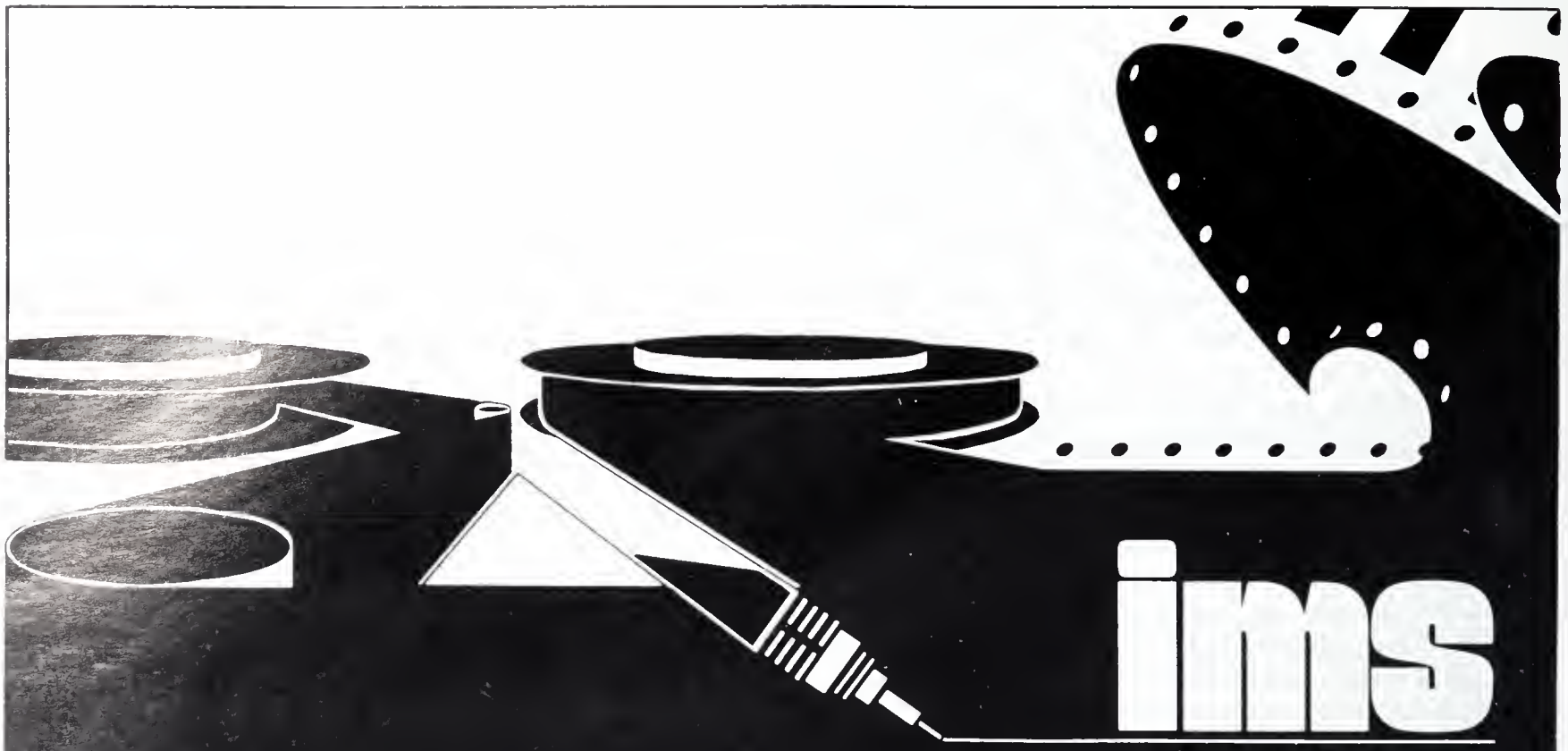

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CARDIOLOGY

Takayasu's Arteritis: The Pulseless Disease

Dele Davies 8T5

As first described in 1908 by M. Takayasu[1], a Japanese ophthalmologist, Takayasu's arteritis characteristically affects Oriental females by causing unusual ocular manifestations including cataracts and wreath-like a-v anastomoses surrounding the optic papillae along with absent radial and brachial pulses and so-called "reversed coarctation" of the aorta.

Takayasu's arteritis is also known as:

- Pulseless disease
- Aortic arch syndrome
- Reversed coarctation
- Occlusive thromboarthropathy
- Young female arteritis
- Primary arteritis of aorta
- Aortitis syndrome
- Giant cell arteritis of aorta
- Non-syphilitic aorta[2, 3]

Epidemiology

Most reported cases of Takayasu's arteritis have been from Asia and Africa with most large case studies documenting that Oriental females are affected far more commonly than males.[4] However, a significant number of cases have been reported from Sweden, England and Mexico, with relatively few examples from North America.[3] This disease predominantly affects the ten to fifty year old age group, but cases beginning in infancy or late middle age have been reported.[5, 6, 7] Nonetheless, 90% of patients are less than thirty years old with 80-90% being females.[5]

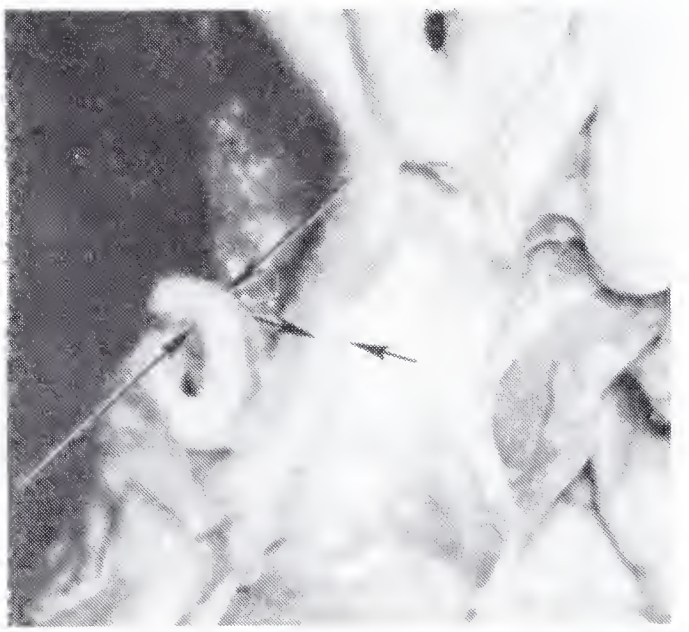
Etiology

The cause of Takayasu's disease remains very elusive. It has been associated with rheumatoid arthritis and other collagen vascular diseases.[2] Up to 80% of patients are reported to have an associated tuberculous infection.[8] Other investigators have also reported a significantly higher incidence of PPD skin reactivity to both *Mycobacterium tuberculosis* and atypical mycobacteria in patients with Takayasu's compared with the population at large.[9] However, tubercle bacilli have never been found in the lesions.

A possible immunologic origin of Takayasu's arteritis is suggested by its predilection for younger females, occasional positive tests for rheumatoid and lupus cell factors and hyperglobulinemia.[3] Also, many patients have myalgic and arthritic symtoms, which respond to steroids. Circulating antiaortic arch antibodies have been detected in Takayasu's patients but it is not known if this is a response to some primary form of arterial injury or an autoimmune reaction.[2] Finally, Takayasu's arteritis has been associated with two B cell alloantigens, HLA-DR4 (70% frequency in cases in one study, 27% in controls) and HLA-MB3 (100% frequency in the same study, 53% in controls).[10] These two antigens are prevalent in Asians.

Pathology

The gross morphological changes in most cases consist of irregular thickening of the aortic wall with internal wrinkling[3] (Fig. 1).



A.

B.

Fig. 1 Neonate arteriopathy in a girl, 10 weeks old who died following much vomiting: hypertrophic pyloric stenosis was operated upon at 8 weeks. At autopsy, the pulmonary trunk, aorta, and their main branches were greatly thickened by elastic hyperplasia. (A) Thickened pulmonary trunk (long arrows), aorta (short arrows), and arch branches (at top). (B) Abdominal aorta showing thickening which extends into branches.[19]

Microscopically, there is an adventitial mononuclear infiltrate with perivascular cuffing of the vasa-vasorum reminiscent of syphilitic aortitis. However, unlike the latter, adventitial changes are accompanied by a diffuse polymorphonuclear infiltrate and, later, a mononuclear medial infiltrate. Caseating granulomas sometimes appear in the media identical to either tuberculosis or giant cell arteritis lesions. Later, there is extensive medial fibrosis and a marked cellular collagenous thickening of the intima. The fibrous reaction thickens the aortic wall and extends into the proximal segments of the aortic branches, reducing their lumina to tiny orifices.[3] Late complications include: localized aneurysm formation, post stenotic dilatation and calcification of the aorta and arterial wall.[2]

Four types of Takayasu's arteritis are known.[5] (Fig. 2).

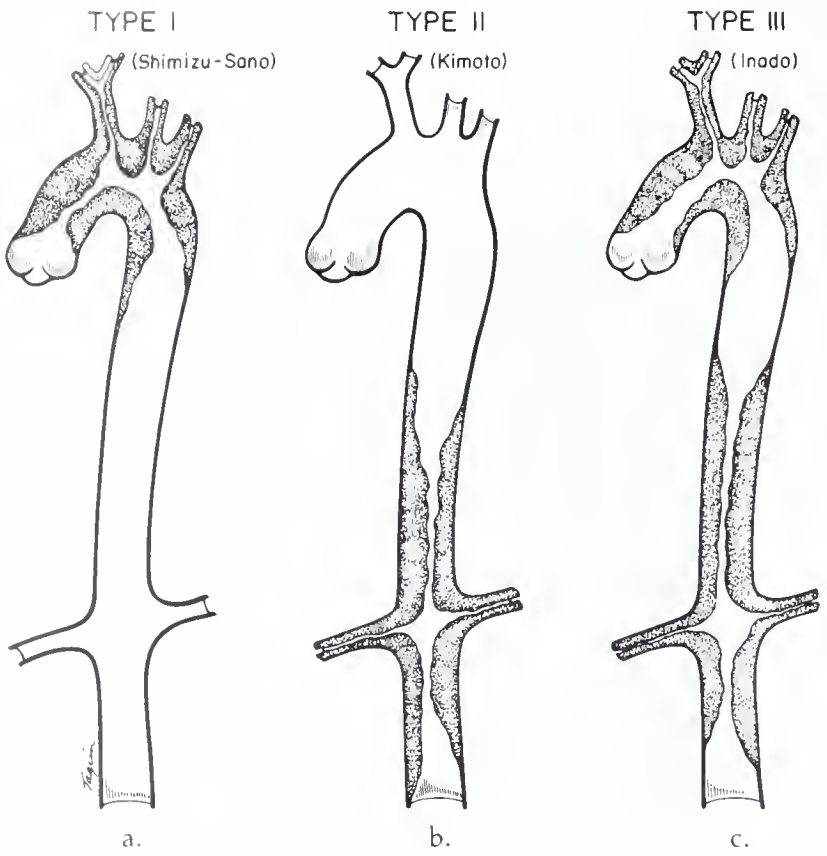


Fig. 2 Types of Takayasu's arteritis. Type I involves primarily the aortic arch and brachiocephalic vessels. Type II affects the thoracoabdominal aorta and particularly the renal arteries. Type III combines features of both types I and II. Types I and III may be complicated by aortic regurgitation. The eponyms for each type are noted.[2]

Eight percent of patients have Type I or Shimizu-Sano type which was described in 1951[11] as the fascinating yet serious "pulseless disease". This disease is characterized by active or chronic inflammation of the ascending aorta, the arch and the great vessels leading to obliteration of the orifices and thus pulseless brachial and radial arteries. (Fig. 2a)

Type II, the Kimoto type, is sometimes referred to as atypical coarctation because stenosis spares the aortic arch but involves the thoracoabdominal aorta and branches.[10] This accounts for 11% of cases.[5] (Fig. 2b)

Type III is the most common (65%)[5] of Takayasu's arteritis types. It involves a combination of the aortic arch and its branches and the thoracoabdominal artery.

Lastly, type IV combines any of types I to III, but also involves the pulmonary artery. 45-50%[5] of all cases described are of Type IV.

Clinical Features

Takayasu's arteritis affects mostly (80-90%)[5] females with 90% of these being less than thirty years old. There are two main phases to this disease.[2] In phase I, 50-60%[2] of patients develop an initial systemic illness lasting from weeks to months. This systemic phase is characterized by fever, anorexia, malaise, weight loss, nausea, night sweats and arthralgia. There may be localized pain and tenderness over affected arteries.

Phase I subsides and all patients, whether or not they went through the systemic phase, enter phase II after a variable latent period.[2] Phase II symptoms are a direct consequence of the stenotic and inflammatory changes in the vessels and are therefore late manifestations of the disease. The signs include (a) diminished or absent pulses (96%), (b) hypertension (74%), (c) bruits (94%), (d) heart failure (28%) and (e) retinopathy (25%).[5] Retinopathy is a sign of carotid artery involvement and may include retinal hemorrhages, iris atrophy, and total blindness. (Fig. 3)

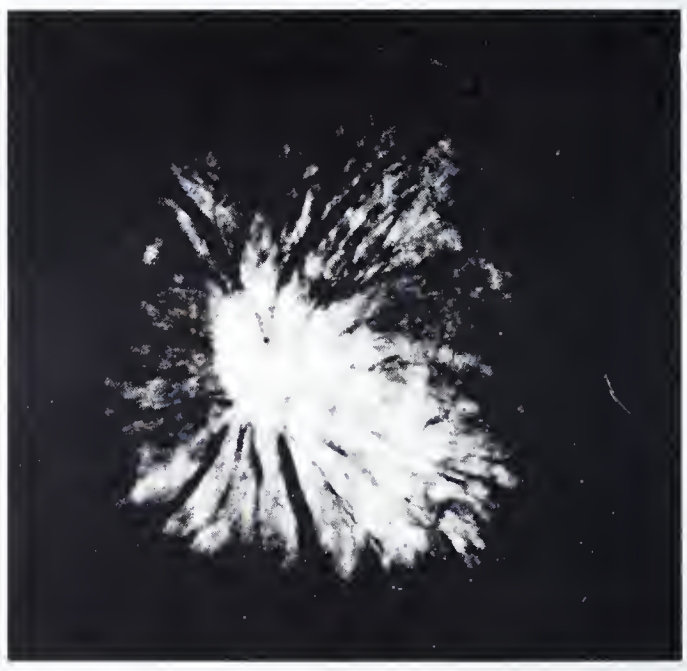


Fig. 3 Proliferative retinopathy of Takayasu's arteritis. This patient was a 27 year old Oriental woman with postural amaurosis and hemiplegia. Brachial pulses were absent.[23]

Other neurological deficits are possible ranging from syncope, dizziness, focal weakness and paraesthesias to complete hemiparesis.[3]

The most typical findings of Takayasu's arteritis the so called "reversed coarctation" or "pulseless disease" are found in patients with Type I and Type III disease. This is characterized by absent or diminished upper body pulses, barely detectable blood pressure in arms, higher pressure in lower extremities, bruits overlying diseased arteries, ischemic manifestations at various sites and syncope.

In Type II patients with the "atypical coarctation", there may be abdominal angina, limb claudication and hypertension due to renal arterial involvement.[2] Several mechanisms may account for the hypertension, the two most important being the hemodynamically significant aortic coarctation and the renal artery stenosis. The reduction of baroreceptor reactivity and decreased aortic capacitance may be further factors.[12,13]

When heart failure is present, it tends to be in the younger age group as a result of systemic hypertension. Rarely, severe hypertension or inflammation and scarring of the aortic valve may lead to aortic regurgitation causing heart failure.[14, 15] Angina and myocardial infarction are due to involvement of the ostia and proximal segments of the coronary arteries.[16, 17]

Investigations

Laboratory investigations show that during the systemic phase, there is frequently an elevated ESR, a low grade leukocytosis and a mild anemia which resolves as the phase subsides.[9] IgG is almost always elevated.[2] Non-specific but common finding include increases in C-reactive protein, anti-streptolysin O titres, and, occasionally, rheumatoid factor and anti-nuclear antibodies.

The chest radiograph is usually normal with an occasional rim of calcification seen in the walls of the affected arteries. The diagnosis is confirmed by arteriography.[18] There is an irregular intimal surface with stenosis of the aorta and/or its tributary arteries, post-stenotic dilatations, saccular aneurysms and occasional vascular occlusions.[2] The thoracic aorta, when affected, has a typical narrowed, "rat tail" appearance on angiography.[18] (Fig. 4). Biopsy may help with the diagnosis.[19]

Fig. 4 Retrograde Thoracic Aortogram demonstrating irregular narrowing of a long segment of the descending aorta, beginning just below the isthmus. Note the typical "rat tail" appearance of the descending thoracic aorta. The arrows denote the extent of the lesions. The ascending aorta and the brachiocephalic branches are normal. This 28 year old woman presented with features of "atypical coarctation" of the aorta that turned out to be Takayasu's arteritis.[10]

Treatment and Prognosis

In the systemic phase, adrenocorticosteroids are very effective in relief of constitutional symptoms such as fever, malaise and fatigue.[20] The erythrocyte sedimentation rate (ESR), which is a very sensitive indicator of activity of the disease, drops towards normal when using prednisone 30 mg/day and tapering to a maintenance dose of 5-10 mg/day.[10] Corticosteroids may also slow down the progression of actual narrowing during the active stage of the disease.[2]

Anticoagulants, of both the warfarin family and platelet inhibitors (aspirin and dipyridamole) are recommended to treat transient ischemic attacks and prevent progression of disease.[2] There is no report of cytoxic drugs being tried.

Surgical techniques including endarterectomy bypass of obstructed arteries (especially the renal arteries), resection of localized coarctations, excision of saccular aneurysms and rarely aortic valve replacement may be required to relieve late complications.[21]

Prognosis for Takayasu's disease is very variable. There is usually a slow progression from months to years. In one large series reviewed by Sunamori,[22] the five year survival after diagnosis was about 83% with heart failure and cerebral vascular accident being the commonest causes of death.

Conclusion

In conclusion, Takayasu's arteritis remains very much a mystery requiring more research to give clues to its etiology treatment and probable management. The three forerunners with regards to cause appear to be infective, immunologic and multiple causes. Perhaps as the field of immunology expands and advances are made, strides will be made in the search for clues in unravelling this mysterious and unfortunate disease and perhaps yield an insight into avenues for more effective therapy.□

References

1. Takayasu M.: Case with unusual changes of the central vessels in the retina. *Acta. Soc. Ophth. Jap. 12*:554, 1908.
2. Heart Disease: A Textbook of Cardiovascular Medicine. E. Braunwald ed. W.B. Saunders Co., 1980.
3. Robbins S.M., Cotran R.S.: Pathologic Basis of Disease, 2nd ed. W.B. Saunders Co., 1979.
4. McKusick V.: A form of vascular disease relatively frequent in the Orient. *Am. Heart J. 63*:57, 1962.
5. Lupi-Herrera E., Sanchez-Torres G., Marcus L. *et al.*: Takayasu's arteritis. Clinical Study of 107 cases. *Am. Heart J. 93*:94, 1977.
6. Inada K., Shimizu H., and Yokoyama T.: Pulseless disease and atypical coarctation of the aorta. *Surgery 52*:133, 1962.
7. Anan P.N., *et al.*: Takayasu's disease. A case report. *Indian Heart J. 29*:568, 1976.
8. Kinare S.G.: Aortitis in early life in India and its association with tuberculosis. *J. Pathol. 100*:69-76, 1970.
9. Nakao K., *et al.*: Takayasu's arteritis. Clinical report of eighty four cases and immunological studies of seven cases. *Circulation 35*:1141, 1967.

10. Sally R.E., *et al.*: Case Report of Mass. Gen. Hosp.: Takayasu's arteritis, *New Engl. J. Med. 299:*1003, 1978.

11. Shimizu K., Sano K.: Pulseless disease. *J. Neuropath. Clin. Neurol. 1:*37-47, 1951.

12. Swinton N.W., Cook G.A.: Systolic hypertension and cardiac mortality of Takayasu's aortoarteritis. *Angiology 27:*568, 1976.

13. Takishita A., *et al.*: Baroreflex sensitivity in patients with Takayasu's aortitis. *Circulation 55:*803, 1977.

14. Chertlin M.D., Carter P.B.: Takayasu's disease - Unusual manifestations. *Arch. Intern. Med. 116:*283, 1965.

15. Honig H.S., *et al.*: Severe aortic regurgitation secondary to idiopathic aortitis. *Am. J. Med. 63:*623, 1977.

16. Pasternac A., *et al.*: Primary arteritis in Takayasu's disease. A case studied by selective coronary arteriography. *Am. J. Roentgenol. 128:*488, 1971.

17. Cipriano P.R., *et al.*: Coronary arterial narrowing in Takayasu's aortitis. *Am. J. Cardiol. 39:*744, 1977.

18. Lande A., Rossi P.: The value of total aortography in the diagnosis of Takayasu's arteritis. *Radiology 114:*287, 1975.

19. Hudson, Reginald E.B.: Cardiovascular Pathology, Vol. 3, Williams and Wilkins Co., Baltimore, 1970.

20. Bonvestre M.V.: Takayasu's disease revisited. *N.Y. State J. Med 74:*1960, 1974.

21. Austen W.G., Shaw R.S.: Surgical treatment of pulseless (Takayasu's) disease. *New Eng. J. Med. 270:*1228, 1964.

22. Sunamori M., *et al.*: Aortitis syndrome due to Takayasu's disease. A guideline for the surgical indications. *J. Cardiovascular Surg. 17:*443, 1976.

23. Cogan D.G.: Ophthalmic Manifestations of Systemic Vascular Disease. Philadelphia, W.B. Saunders Co., 52, 1974.

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PLASTIC SURGERY

Topical Nutrients in Wound Healing

Eben Stern 8T5, Stanley Zlotkin, M.D., F.R.C.P. (C), and Ronald Zuker, M.D., F.R.C.S. (C)

Wound healing has been a fertile area of research as great advances have been made in systemic and topical antibiotics to improve wound healing by keeping the wound clean.[1] In spite of these advances, the issue remains whether or not the wound healing process is operating at its maximum efficiency if the wound is simply maintained free of contamination. In other words, can wound healing be accelerated from its infection-free rate? This study sets out to evaluate the role of topical nutrients in wound healing, using proper controls.

The literature involving topical nutrients and wound healing is sparse. Some studies have claimed success with topical sugar, along with amino acids or povidone-iodine, used primarily in infected wounds.[1-3] Knutson *et al.* used sugar on fresh wounds and also claimed that these wounds healed faster than those treated by the conventional methods.[3] However, no proper controls were ever used in any of these human studies, and thus, the validity of their claims is questionable.

Examining this question more closely, one turns to such evidence as the inhibition of wound healing by necrotic tissue and ischemia.[1] If nutrients have trouble reaching healing tissue via the bloodstream, wound healing should be retarded. Therefore, it seems reasonable to assess the capability of topical nutrients to accelerate healing.

The logic behind the nutrients chosen was as follows:

Sugar
- is an acid and thus, it is a vasodilator[3]; vasodilation increases oxygen delivery, as well as general nutrient delivery. Oxygen delivery is of prime importance as oxygen is a cofactor in the rate limiting step of collagen synthesis (prolyl hydroxylation).[4]
- has a hydroscopic effect and thus, it decreases edema.[3] Decreased edema decreases the distance that blood-borne nutrients have to travel to reach the site of injury.
- possibly provides nutrients for healing tissue.

Amino acids
- are building blocks for proteins[4], and are of chief importance in the wound healing process for the collagen synthesized by fibroblasts.

Ascorbic acid
- is a cofactor in the rate limiting step of collagen synthesis

Methods and Manipulations

Four 4 kg Reimans rabbits, three female and one male, had their backs shaven and prepared. Using a sterile procedure, two 3 x 3 cm^2 areas, each area on opposite sides 3 cm from the midline, were excised down to and including the panniculus carnosus. After excision, the areas were 3½-4 x 3½-4 cm^2. Using a marker on transparencies, the areas of the wounds were measured initially, and then on a regular basis throughout the study. This proved to be an easy and accurate method of assessing wound area.

On the test wound, topical nutrients were applied, while on the control wound saline was used. Each rabbit served as its own control to abolish the inter-rabbit variables. The test wound was treated every Monday, Wednesday, and Friday morning with 10 cc. of a standard amino acid solution, Aminosyn, followed by three spatulas, or 2.5 g of a glucose polymer powder with added 3% ascorbic acid. The control wound was treated every Monday, Wednesday, and Friday morning with 10 cc. of 0.9% sodium choride irrigation. The wounds were dressed with sterile gauze, cling, and elastoplast. When the wounds began to scab over, plastic was applied over the gauze to keep the wound moist so that the solution, the powder and saline would reach the wound. If the plastic was not effective (the rabbits sometimes unwound their dressings causing the wounds to scab over) the scabs were moistened with saline and carefully removed, under anaesthetic if they did not peel off easily. All animals were weighed at the beginning and end of the study to ensure that no substantial weight was lost.

Results

The average length of observation was 22 days. In all rabbits, the test wounds did not heal more rapidly than the control wounds; in fact, in one rabbit, the control wound healed better than the test wound. In this rabbit, the study ended after 21 days. Five days previously, the control wound was level with the rest of the skin with the defect completely filled. The wound area was 1.2 x 1.6 cm^2. At 21 days, the wound size was 1 x 4 mm^2. On the other hand, five days previously, the test wound had a 1 x 1.7 cm^2 hollow remaining to be filled. The wound area was 1.9 x 2 cm^2. At 21 days, the evidence of the wound was a 1.2 x 1.4 cm^2 area.

Only one rabbit lost substantial weight (0.35 kg) during the study.

Discussion

This study supports the hypothesis that topically applied glucose, ascorbic acid, and amino acids in the quantities stated do not increase the rate of wound healing in healthy rabbits.

The investigations with topical nutrients which continued after this study were completed with two modifications. Firstly, the percentage of ascorbic acid in the glucose polymer

powder was increased to 10% as the 3% in the initial powder would perhaps not allow the effects of ascorbic acid to display their worth. Secondly, one spatula, or 1 g, of glycine crystals was applied after the amino acid solution and before the powder. The amino acid composition of collagen has the general formula Gly-X-Y;[4] in other words, every third amino acid in collagen is glycine. It was felt that by adding glycine crystals in excess, in addition to the amount in the amino acid solution, the effect of glycine on new collagen formation would perhaps manifest itself.

The results of this new study once again support the same negative conclusion.

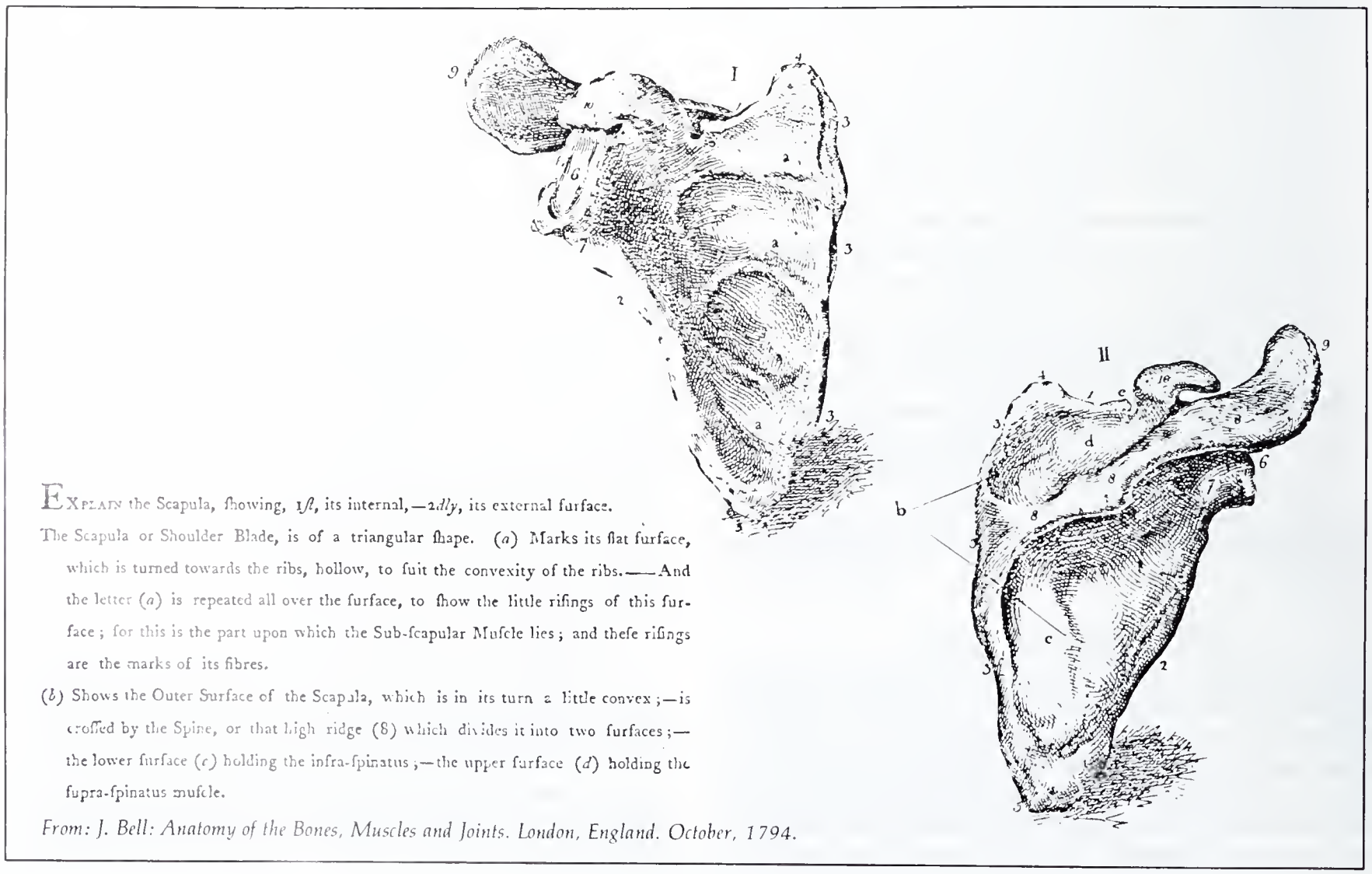
There are several possible explanations for the obtained results. Perhaps, the nutrients in the bloodstream reaching the healing tissue are adequate for maximum rate of healing; thus, the topical nutrients were superfluous. Or perhaps, fibroblasts are incapable of utilizing topical amino acids for collagen synthesis because of saturated uptake mechanism. Another possible explanation is that sugar is an insignificant vasodilator, and even if it is significant, vasodilatation may not be as vital in wound healing as one would believe; Pai and Hunt illustrated that subjects breathing 45% oxygen at 1 atmosphere increased their rate of wound healing up to a maximum of only 15%.[5]

One last explanation is a very important one. Wound healing involves various complexities. The study concentrated on attempting to increase collagen synthesis, but one must also be aware that the wound healing process also involves contraction of the wound margins, migration of epithelial cells, and the ingrowth of new vasculature.[6] Increased knowledge is essential in these other processes of wound healing in order to understand the healing process as a whole. Once this knowledge is gained, the answer to the original question will be closer to realization.

It is unreasonable to extrapolate the results from this study to the human subject, but if these findings are applicable to the human, then this study emphasizes something of general significance. In this era of modern medical technology when we constantly turn to external resources in the form of various antibiotics and supplements to treat a variety of illnesses, it is a relief from this pattern of external aid to realize that the normal human architecture possesses the ability to heal the type of wounds inflicted in this study at a maximum rate without supplemental intervention, so long as the wound is kept sterile.□

References

1. Silvetti, A.N.: An effective method of treating long-enduring wounds and ulcers by topical application of solutions of nutrients. *J. Dermatol. Surg. Oncol. 7*:501, 1981.
2. Medical News. Sugar sweetens the lot of patients in bedsores. Ed. J. Kangilaski. *JAMA 223*:22, 1973.
3. Knutson, R.A., Merbitz, L.A., Creekmore, M.A., and Snipes, G.H.: Use of sugar and povidone-iodine to enhance wound healing: five years' experience. *South. Med. J. 74*:1329, 1981.
4. Principles of Biochemistry. Ed. A. White *et al.* New York, MacGraw-Hill, Inc. 6th Ed., 1978.
5. Pai, M.P. and Hunt, T.K.: Effect of varying oxygen tensions on healing of open wounds. *Surg. Gyn. and Obs. 135*:756, 1981.
6. Pathology. Ed.: W.A.D. Anderson and J.M. Kissane. St. Louis, The C.V. Mosby Co., 7th Ed., 1977.



EXPLAIN the Scapula, ſhowing, 1ſt, its internal,—2dly, its external ſurface.

The Scapula or Shoulder Blade, is of a triangular ſhape. (*a*) Marks its flat ſurface, which is turned towards the ribs, hollow, to ſuit the convexity of the ribs.——And the letter (*a*) is repeated all over the ſurface, to ſhow the little riſings of this ſurface; for this is the part upon which the Sub-ſcapular Muſcle lies; and theſe riſings are the marks of its fibres.

(*b*) Shows the Outer Surface of the Scapula, which is in its turn a little convex;—is croſſed by the Spine, or that high ridge (8) which divides it into two ſurfaces;—the lower ſurface (*c*) holding the infra-ſpinatus;—the upper ſurface (*d*) holding the ſupra-ſpinatus muſcle.

From: J. Bell: Anatomy of the Bones, Muscles and Joints. London, England. October, 1794.

COMPUTERS IN MEDICINE

Computers and Medical Education Part I: The Future is Now

Paul H. Marks 8T6 and Paul E. Rosen*

Computers are becoming increasingly important in the practice of medicine and the delivery of health services. The need for effective management of health data is important for financial and health information reasons. If a health computer system is to be implemented successfully, health professionals must become computer literate. Acceptance of new technology requires a process of education on many levels. A discussion of Computer Assisted Instruction (CAI) and a proposed outline for a course in medical computer applications has been included.

Physicians of the future will be inundated by information and population explosions. Computers will surely have a significant role to play in helping physicians deal with these problems. A positive attitude toward this instrument can be developed by viewing the computer as another "tool in the little black bag". The purpose of this "electronic assistant" will be to save the practising physician time and increase his or her productivity and clinical accuracy. At the same time, it will facilitate completeness and scope of health examination and its assessment, while reducing the cost of health care.

Acceptance of this technology requires a process of education at several levels. The "users", who will include physicians, medical and paramedical personnel, must understand, accept and participate in the planning of these systems. They must at least become computer knowledgeable.

There are two major issues in dealing with computers and medical education. The first issue is the use of Computer Aided Instruction (C.A.I.) and Computer Assisted Learning (C.A.L.). The second is the teaching of medical computer applications to medical students.

Computer Aided Instruction (CAI) and Computer Assisted Learning (CAL) have been introduced slowly into the curricula of major medical schools over the last twenty years. Many universities are past the decision-making phase, and are pursuing the problem-solving phase: they are not deciding *whether* but rather *how* computers are to be integrated into their teaching program.

There is a good rationale for this. CAI is a flexible, powerful, and potientially cost-effective method of instruction, with a great number of applications and benefits. By using the computer as a "teacher", students are free to learn at their own pace, whether it be fast or slow. Graphs, charts, and diagrams can be screened and changed at a moment's notice, providing the student with instant feedback. Step-by-step corrective coaching can be accomplished without the strain on a teacher's patience. Finally, one computer can teach hundreds of students on an ongoing basis, and is limited only by the size of the computer memory and the number of terminals available for use.

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By far the most common form of CAI, and the most advantageous use of the computer's features, is dynamic simulation. Through a combination of text and diagram, a student is led through a pathway that changes in response to his or her actions. The advantage of a computer in this case is that changes and feedback can be produced immediately and with the enormous amount of information that can be stored, the complexity of the program depends only on the programmer's knowledge and ability. (See Fig. 1)[18].

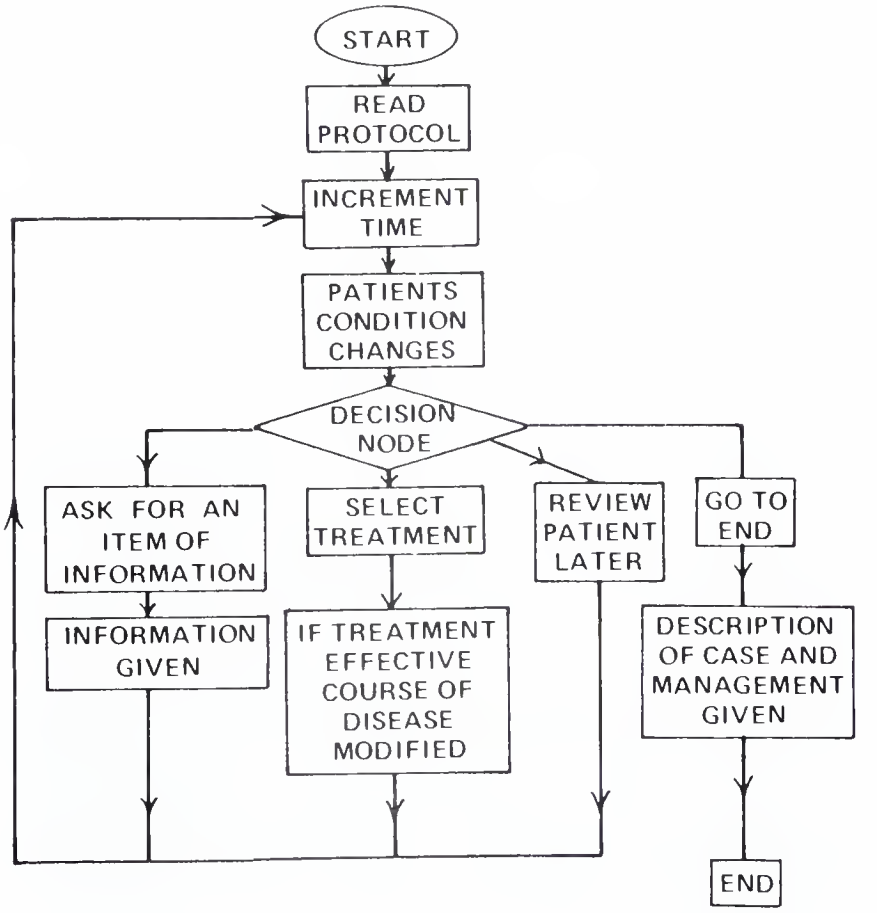

Fig. 1. Flow diagram showing pathways through a typical dynamic simulation program.[18]

Simulation programs have been written for many disciplines. Although they lend themselves well to scientific and mathematical studies, other subjects can be approached in this manner, such as economics, sociology, business management and psychology.[19] In fact, it is only the interests of the programmer and the time available that determine what is currently available in CAI.

The medical field is especially attuned to the possibility of large-scale use of computers for training. In addition to teaching basic sciences, a CAI-equipped medical school provides its students with the closest simulation of real clinical decision-making experiences short of the clinical environment itself. A number of recent articles have been published on the enhancement of decision-making ability exhibited by medical students after participating in computer simulation exercises.[1,2] Through these and other studies, knowledge is gradually accumulating about the effectiveness of CAI in the medical environment and the possibilities for a variety of applications.

The range of subjects is as great as the range of medical schools utilizing them. Physiology is taught by computer at both Chelsea College in London[4] and University of the Witwatersrand in South Africa [3], with a Gross Anatomy program without dissection being offered at Emory University in Atlanta.[5] There are basic science courses that differ little from traditional "programmed learning" courses being offered at the Universities of Ottawa[6], Connecticut[7], and Western Australia[8], in addition to Harvard University[6]. Simulation programs dealing with patient diagnosis are operating in the Universities of Glasgow[9], Illinois[10], Wisconsin (at Madison)[11], California (at San Diego)[12], Birmingham[13], and St. Bartholomew's Hospital Medical College in London[2]. In addition, there are some innovative, and interesting uses of computers as they relate to education. At the Massachusetts General Hospital, a project was instituted using computers for continuing education of graduate physicians.[14] Cost consciousness for the medical doctor was taught in Brown University's medical program.[15] For those who believe that CAI can be used to benefit students, the University of Alabama has developed a program to store test questions in a "test bank" to generate original tests on demand.[16]

It is observable from the foregoing examples that many important medical institutions are involved with CAI in a variety of ways. But what of the attitudes toward CAI?

In most cases, the attitude towards CAI by students is uniformly positive. In one study, where over 300 students had been exposed to computer simulation instruction, all students participated in an optional additional case history.[17] Medical students seem to enjoy the clinical simulation and the small group interaction that accompanies most CAI programs.

There have been instances of negative reaction to such systems. Most of these derive from the difficulty of the program language, which made interaction with the computer difficult, and from technical difficulties such as those to be encountered by students unfamiliar with computer operation.[6] As knowledge of the requirements for this type of instruction increases, there are fewer reported incidents of user difficulty.

For the most part, educators have also been enthusiastic about CAI. However, there are questions that are raised repeatedly that have yet to be answered. The first concerns the amount of learning benefit actually enjoyed by the students as compared to traditional formats. Some studies show a difference in learning in the computer user group as compared to the conventionally taught students, ranging from no significant statistical gain,[10] to up to three times the increase in performance in the control group.[2] As yet, there has not been a sufficient amount of information on the subject with which to make an accurate analysis, but indications are that computer assisted instruction is at least as effective as conventional teaching techniques for producing learning.

A second question that must be addressed is that of actual cost effectiveness for the medical teaching institution. Since there has been such a wide variation in hardware and software utilized for this purpose, standardized assessment does not exist. This information is vital to large-scale implementation of such systems.

Other questions include those dealing with computer simulation. Are simulations realistic in terms of the situations that a student will encounter in clinical practice? Are they useful in terms of teaching decision-making strategies, or do they instruct the student in learning to play the game? How can objective evaluations be carried out using this system of instruction? And, how can differing opinions on the same case be handled, especially as new treatments are developed? Answers must be forthcoming for this instruction to be universally acceptable.

At this time, there is much activity in the medical field concerning CAI, its potential has proved to be great. Simulation programs offer instruction that is not available to the student by other means. Various other applications of computers in a medical teaching environment exist now and can be developed in the future. This medium is ready for implementation by all major medical institutions as a way to keep in step with the most modern and efficient technology that is available. O'Neill, *et al.*[12] recommend that "any system of self-instruction, if it is to be successful, (a) must have complete faculty endorsement, (b) must be confidently accepted by students, and (c) must be specifically tailored to support directly the curriculum (most desirable as a mandatory part of the instructional program)." Without the complete approval of the administrations of these institutions, the other criteria will not be met, and this great potential for innovation in medical education will go unrealized.

In implementing a course in medical computer applications, an important question must be asked: why do medical students and medical school graduates have little or no understanding of computer and information technology? The answer is that the pre-med academic curriculum virtually eliminated the possibility of receiving exposure to computers before entering medical school. It is, therefore, appropriate to introduce into the medical curriculum a brief course in medical computer applications.

The primary objective of such a course would be to give all those students who wish, the opportunity to become computer "literate". Secondary objectives would include:

1. Capturing the attention of the student, to establish firmly his/her interest in computer usage.
2. Acquainting the student with present and possible future uses of computers in medicine.
3. Allowing the student to pursue further any subsequent interests in computer applications to medicine via electives or selectives.
4. Teaching the student computer operation and programming if interest and resources are available.

The Core Program Unit (CPU) of this course would be taught by guest lecturers, who would be either medical scientists or clinicians using computers or computer scientists working on a medical problem and describing their work.

The introductory lectures might consist of topics covering computer costs, reliability, system software, data bases, available programs, patient files, and standardizations. The use of demonstrations or simulations of present or possible future applications would be beneficial. Examples include: biomedical research, simulation of monitoring a patient's respiration, electrocardiogram, and electroencephalogram. Demonstrations could include computer history-taking, computer-assisted diagnosis, drug screening, and information retrieval on computer systems. Depending on resources, an "open shop, hands-on" period during which the student is expected to operate the computer and enter, debug, compile, and execute a simple self-written program could be implemented.

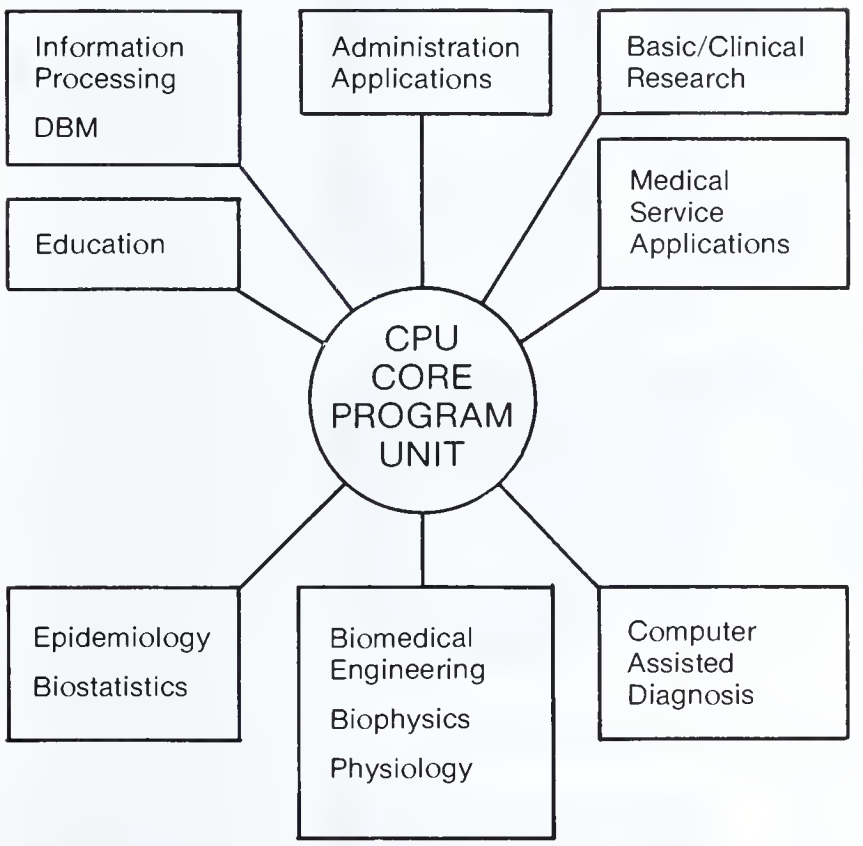

Fig. 2. A proposed overview for a course on computers in medicine.

Once the student has gained a knowledge of computers from the Central Processing Unit (CPU) Core Program (see Fig. 2) it would then be possible to advance to any of the following suggested elective/selective topics:

1. Information processing and data base management.
2. Administration applications including financial accounting, payroll, inventory, dietary services.
3. Basic and clinical research applications.
4. Education applications including the curriculum data base and computer assisted instruction (CAI).
5. Medical service applications including laboratory operation, nuclear medicine, and cardiology.
6. Epidemiology and biostatistics, e.g. cancer registry.
7. Biomedical engineering, biophysics and physiology.
8. Future applications including artificial intelligence and Computer Assisted Diagnosis.

The success of a course in medical computer applications depends fully on the following:

1. Understanding student wants and needs in this area of educational opportunity.
2. Developing a list of possible resource people including students, teachers, clinicians, and scientists, to provide a basis of knowledge.
3. Implementing a modular strategy for maximum flexibility and success.

Computers are at present and will continue to become increasingly important in the practice of medicine. The availability of advanced biomedical technology influences not only the area of health care delivery, but also far-reaching medical, educational, epidemiological, social, economic, and technological applications. It has been said that if the aircraft industry had moved as fast as the computer industry is now moving, they would have gone from the Kitty Hawk to the 747 in six months. A gap in the medical student's training has been identified and an educational proposal has been outlined. THE FUTURE IS NOW! □

References

1. T.S. Murray, R.W. Cupples, J.H. Barber, W.R. Dunn, D.B. Scott and D.R. Hannay: Teaching decision making to medical undergraduates by computer-assisted learning. *Medical Education 11:* 262, 1977.
2. J.B. Skinner, G. Knowles, R.F. Armstrong and D. Ingram: The use of computerized learning in intensive care: an evaluation of a new teaching program. *Medical Education 17:*53, 1983.
3. J.H.F. Meyer and G.R. Beaton: An Evaluation of Computer-Assisted Teaching in Physiology. *Journal of Medical Education 49:* 295, 1974.
4. S. Lal and A.W. Wood: Computer-assisted learning in the teaching of physiology. Proceedings of the Physiological Society, April 1977:11P.
5. N.A. Jones, R.P. Olafson, and J. Sutin: Evaluation of a Gross Anatomy Program Without Dissection. *Journal of Medical Education 53:*198, 1978.
6. D.Z. Levine: Computer-aided instruction at the Ottawa General Hospital. *Medical Education 108:*486, 1973.
7. C.L. Gjerde: Integration of Computers into a Course on Biostatics. *Journal of Medical Education 52:* 687, 1977.
8. B.W. Madsen and R.C. Bell: The development of a computer assisted instruction and assessment system in pharmacology. *Medical Education 11:*13, 1977.
9. T.S. Murray, R.W. Cupples, J.H. Barber, D.R. Hannay, and D.B. Scott: Computer-Assisted Learning in Undergraduate Medical Teaching, *The Lancet,* 494, February 28, 1976.
10. D.L. Essex and W.E. Sorlie: Effectiveness of instructional computers in teaching basic medical sciences. *Medical Education 13:* 189, 1979.
11. R.B. Friedman, D.R. Korst, J.V. Schultz, E. Beatty and S. Entine: Experience with the Simulated Patient-Physician Encounter. *Journal of Medical Education 53: 825, 1978.*
12. T. O'Neill, J. Sewall and R. Marchand: Time-Shared Computer-Assisted Preclinical Instruction: A Short Trial and Evaluation. *Journal of Medical Education 51:* 766, 1976.

13. P.P. Raj, L.J. Kricka and A.J. Clewett: Microcomputer simulations as aids in medical education: application in clinical chemistry. *Medical Education 16:*333, 1982.

14. E.P. Hoffer: Computer-Aided Instruction in Community Hospital Emergency Departments: A Pilot Project. *Journal of Medical Education. 50:*84, 1975.

15. S.R. Smith: An Evaluation of a Computerized Exercise in Teaching Cost Consciousness. *Journal of Medical Education 58:*146, 1983.

16. C.M. Brooks, W.E. Dismukes, G.R. Williams and S. Brown: A computer-based test item-bank for cognitive assessment of medical students during medicine clerkship. *Medical Education 16:*12, 1982.

17. T.S. Murray, J.H. Barber and W.R. Dunn: Attitudes of medical undergraduates in Glasgow to computer-assisted learning. *Medical Education 12:*8, 1978.

18. A.E. Dugdale, D. Chandler and G. Best: Teaching the management of medical emergencies using an interactive computer terminal. *Medical Education 16:* 27-30, 1982.

19. *Pipeline*, Volume 8, Number 1, Spring 1983, University of Iowa, Iowa City, U.S.A.

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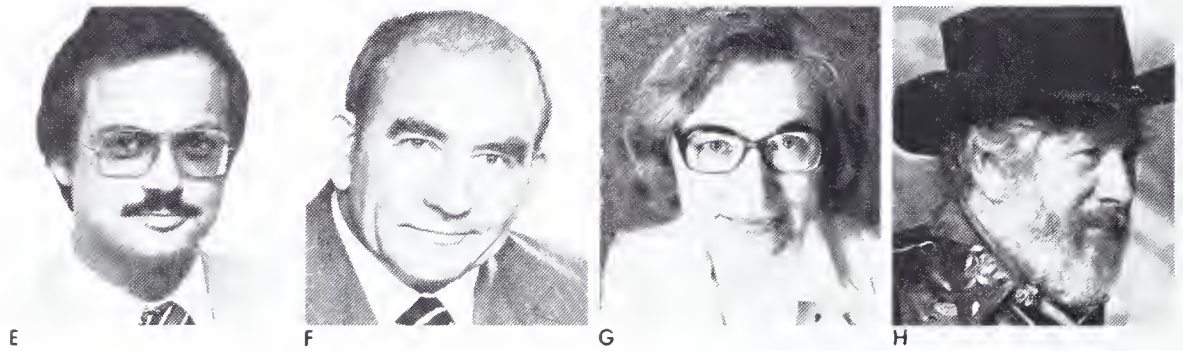

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RADIOLOGY

A Radiological Review of Hodgkin's Disease

Bernard Boulanger 8T5

Hodgkin's Disease (HD) is an uncommon disorder of the immune system with well-described clinical and pathological features. HD represents 1% of all human cancers and the pathological and radiological findings are primarily confined to the lymphoid tissue of the body. With the development of more sophisticated chemotherapeutic and radiotherapeutic techniques over the last 25 years, the prognosis for patients with HD has improved dramatically. The therapeutic regimen chosen for a particular patient depends on the histological sub-type of HD and the stage of the disease. Since staging laparotomies are not routinely performed in Toronto, HD is staged primarily by imaging techniques. The imaging techniques in present use are: plain films, computed tomography (CT), conventional tomography, ultrasonography, bipedal lymphangiography (LAG) and radioisotopic studies. In this paper, the radiological presentation and staging of HD will be discussed with a brief review of the clinical and pathological aspects of HD.

Introduction

Hodgkin's Disease (HD) was first described as a clinical and pathological entity by Thomas Hodgkin in the early 1800's.[1] The etiology and pathogenesis remain unknown.

HD comprises 40% of lymphomas in patients of all ages. This disease has a bimodal age-specific incidence with peaks between 15-34 years of age and over 50 years of age. Although HD represents 1% of all cancer cases it accounts for 17% of cancer cases in the age interval 15-34 years. HD has a world-wide distribution with a slight predilection for males.[2]

The diagnosis of Hodgkin's Disease is made on pathological grounds. In the typical case, a superficial area of lymphadenopathy is biopsied, and the diagnosis of HD is made upon microscopic examination of the specimen. The next step in the proper management of a patient with HD is to determine the extent or stage of the disease. The therapy chosen, radiotherapy, chemotherapy, or combination therapy, depends on the histological sub-type of HD and the stage of the disease. Various radiological modalities are employed in the assessment and staging of HD: plain films, computed tomography (CT), conventional tomography, ultrasonography, bipedal lymphangiography (LAG) and radioisotopic studies. In this paper, the contribution of each of these imaging techniques to the management of patients with HD will be discussed. As well, pertinent clinical and pathological features of HD will be reviewed.

Pathology

The definitive diagnosis of Hodgkin's Lymphoma can only be made after tissue biopsy. The most commonly biopsied sites are: areas of palpable lymphadenopathy, a retroperitoneal or mediastinal mass, bone marrow, liver and spleen.

Any organ or structure in the body may eventually become involved with HD. The commonest sites of pathological importance are: the cervical, axillary, supraclavicular, mediastinal, hilar, retroperitoneal and inguinal lymph nodes, the spleen, liver and bone marrow. In general, the nodal lesions take the form of confluent, lobulated, irregular masses. Hepatic and splenic involvement varies form large confluent masses to diffuse tumor inflitration.

Unlike Non-Hodgkin's lymphoma, the lymphoid tissue of Waldeyer's ring, the G.I. tract and the mesenteric, popliteal and epitrochlear nodes are very rarely involved with HD. The thymus has been reported as the sole site of HD, especially in young patients.[3]

Primary lymphomatous involvement of the liver is rare and secondary hepatic lesions are very uncommon in the absence of splenic lesions. Mediastinal lymphadenopathy is extremely common, especially in the nodular sclerosing type, and is often accompanied by unilateral or bilateral hilar lymphadenopathy. Although HD can involve the pulmonary parenchyma, it rarely presents there initially without concomitant mediastinal or ipsilateral hilar lymphadenopathy.

In one series, 6-14% of previously untreated cases of HD had positive bone marrow biopsies.[4] The incidence of bone marrow involvement increases if the disease is uncontrolled by treatment. Bony lesions can be osteoblastic, osteolytic, or mixed. The majority of skeletal lesions are in the axial skeleton and proximal femur.

There are four histological sub-types of HD defined by the Rye Conference classification scheme (1965).[5] Each histological sub-type has varying numbers of Reed-Sternberg cells, the characteristic Hodgkin's cell. The Rye Classification is well accepted and prognostically valuable. The four sub-types are: lymphocyte-predominance HD (LPHD), mixed cellularity HD (MCHD), lymphocyte-depletion HD (LDHD) and nodular sclerosing HD (NSHD). The more extensive the lymphocytic infiltrate, the more favourable is the prognosis. The most common histological patterns are the nodular sclerosing and mixed-cellularity types. The majority of young patients have NSHD. MCHD and LDHD are more aggressive conditions than LPHD and NSHD. Intra-abdominal nodes are more commonly involved with the MC and LD types. NSHD has a predilection for mediastinal nodes, whereas, IPHD rarely affects the mediastimum.[6]

Clinical Considerations

The commonest clinical presentation of HD is painless cervical lymphadenopathy, with or without constitutional symptoms. The constitutional symptoms of prognostic importance

are: fever, night sweats and a 10% weight loss over the preceding six months. These three symptoms are known as the B symptoms and are associated with a poor prognosis (Table 1). Other symptoms of HD of less prognostic importance are: fatigue, anorexia, pain in areas of lymphadenopathy with ingestion of alcoholic beverages, cachexia, weakness and generalized pruritus.

Table I. — **Hodgkin's Disease: Ann Arbor Clinical Staging Classification**

Stage	Characteristics
I	Involvement of a single lymph node region (I) or of a single extralymphatic organ or site (I_E)
II	Involvement limited to one side of the diaphragm, either of two lymph node regions, or localized involvement of an extralymphatic site and one lymph node regions
III	Involvement of lymph node regions on both sides of the diaphragm, which may include localized involvement of an extralymphatic site or spleen
IV	Diffuse or disseminated involvement of one extralymphatic organ or any liver involvement, with or without associated lymph node involvement
	Each case is further classified as:
A	If asymptomatic
B	If any of the following are present: — unexplained weight loss of more than 10% of body weight in the preceding 6 months — unexplained fever, with temperatures above 38°C — night sweats

From Carbone, P.T. et al.: Staging in Hodgkin's Disease (Symposium Ann Arbor), Cancer Res. 31:1707, 1971.

Mediastinal and/or hilar lymphadenopathy due to HD may present as an asymptomatic patient with a positive chest x-ray, a non-productive cough, SVC obstruction, Horner's Syndrome, laryngeal paralysis, or dysphagia.

Intra-abdominal or intra-pelvic lymphadenopathy may present as: a palpable mass, pyrexia of unknown origin or obstruction of the IVC, biliary tract or ureter(s). Otherwise, involvement of retroperitoneal nodes is often discovered when a patient with biopsy-proven HD undergoes staging for abdominal disease.

HD can spread from lymphatic structures to almost any organ in the body, hematogenously or by direct extension. The extension of lymphomatous involvement from a node or nodal group to contiguous nodes or structures is characteristic of HD. If blood vessel invasion occurs, hematogenous spread most commonly results in hepatic, splenic and bony lesions. In 30% of HD cases, the spleen is involved at presentation.[7] Also, 17% of patients with HD develop clinical hepatomegaly sometime during the course of their illness.[8] Bony involvement, although uncommon at the time of initial presentation, may lead to pain at the site, vertebral body compression and rarely fracture. In this respect, spinal cord compression can be the presenting problem in a case of HD.

Modern treatment of HD consists primarily of radiotherapy, chemotherapy or combination therapy. With the development of megavoltage radiotherapeutic techniques in the 1950's, it became possible to deliver high doses of irradiation to specific tissue volumes. Thus, the precise localization of tumor involvement by imaging techniques in the 1950's, it became possible to deliver high doses of irradiation to specific tissue volumes. Thus, the precise localization of tumor involvement by imaging techniques has become more important.

It is generally accepted that radiotherapy is appropriate for Stage IA, IB, II-A, II-B, and some Stage III patients. The role of radiotherapy in the management of other patients with HD remains controversial. Chemotherapy such as the MOPP*, COPP* and ABVD*** regimens, is reserved mainly for patients with Stage III and Stage IV disease.

The prognosis for a patient with HD depends on the anatomic stage at presentation, the histologic sub-type of HD and the presence or absence of B symptoms. Kaplan has reported a 5-yr. survival of 90% for patients with Stage I HD given modern therapy. This is in contrast to a 5-yr. survival of 45% for patients with Stage IV HD.[9] Therefore, radiological determination of the anatomic stage of HD at presentation is valuable as a prognostic tool.

Plain Films

The plain film studies of greatest value in the radiological assessment of HD are the chest PA and lateral films. The commonest presentation of HD on plain chest films is mediastinal and/or hilar lymphadenopathy.[10] It is uncommon to visualize hilar lymphadenopathy without concomitant mediastinal lymphadenopathy. (Figs. 1 and 2). Any of the mediastinal compartments can be involved but the anterior and superior compartments more commonly show disease.[11] Enlarged mediastinal nodes are evident on plain chest films by distortion of the mediastinal pleura or an increase in density of a mediastinal compartment. In this respect, enlarged right and left paratracheal nodes are easier to visualize than enlarged subcarinal or retrotracheal nodes on plain films. The enlarged nodes may appear as discrete lobulations of the mediastinal border or as a scalloped lobulated homogenous mass. Often the appearance of the altered mediastinum is subtle and old chest films are of paramount importance in these cases. It may be difficult to differentiate between mediastinal lymphadenopathy and other causes of a mediastinal mass (aneurysms, teratomas, bronchogenic cysts, etc.) on plain chest films. For these cases, conventional mediastinal tomography or computed tomography (CT) of the mediastinum may contribute additional information.

A broad spectrum of pulmonary parenchymal lesions may occur in HD. These lesions are usually accompanied by ipsilateral hilar lymphadenopathy and are more common with a relapse of HD than at the time of initial diagnosis. On plain films taken at initial presentation, one may see consolidation with air bonchograms, atelectasis, a homogenous nodule or mass, a cavitating lesion (rare), or a perihilar lymphangitic pattern. Calcification of untreated HD pulmonary lesions is rare. Contiguous interstitial spread of the disease into the lung parenchyma from involved hilar nodes (Stage I or II) implies a better prognosis than lymphomatous parenchymal involvement distinct from the hila (Stage IV) (See Figs. 1 and 2).

*MOPP — Nitrogen mustard, Oncovin (Vincristine), Prednisone, Procarbazine
**COPP — Cyclophosphamide, Oncovin, Prednisone, Procarbazine
***ABVD — Adriamycin (Doxorubicin) Bleomycin, Vinblastine, DTIC

Fig. 1

Fig. 1 and 2 PA and lateral chest views of a male with extensive intrathoracic disease due to HD. Anterior and superior mediastinal lymphadenopathy is visualized on the PA and lateral films. A posterior mediastinal mass, representing lymphadenopathy, can be seen on the PA view only (small arrows). Bilateral hilar lymphadenopathy is demonstrated. There is a solitary non-cavitating lesion in the inferior segment of the lingula, best seen on the lateral film (large arrow).

Fig. 2

For a patient with intrathoracic disease related to HD, plain chest films are a fast, non-invasive, inexpensive method to monitor the response of the patient to therapy and to detect progression or recurrence of the disease. Radiation pneumonitis may occur in irradiated lung parenchyma, particularly in the para-mediastinal and apical regions. Classically, this post-irradiation fibrosis presents on plain films as interstitial fibrosis, contraction of the affected segments and a sharp demarcation between irradiated and non-irradiated lung. There may be intrathoracic lesions due to drug toxicity or opportunistic infections. Even by careful examination of previous chest films and with knowledge of the clinical history, one may be unable to distinguish these intrathoracic lesions from progression or recurrence of the tumor. It must be remembered that the development of a pleural effusion during or after radiotherapy is not due to the irradiation and attention should be given to pleural or hilar-mediastinal involvement by HD.

Pleural disease due to HD may be visualized on plain chest films. Pleural effusions are uncommon and when present show malignant cells on cytologic examination in about 15% of cases.[12] These effusions are caused by either obstruction to lymphatic flow by mediastinal and or hilar lymphadenopathy or by direct lymphomatous infiltration of the pleura. A chylothorax (total fat content in pleural fluid greater than 12 mmol/L) is indistinguishable on plain chest films from other forms of pleural effusions, and may occur in HD due to thoracic duct obstruction. Pleural and extra-pleural masses may develop during the course of HD.[11]

The heart very uncommonly becomes involved with HD. The commonest radiologic presentation of cardiac disease is an enlarged cardiac silhouette, due to a pericardial effusion.[11] However, on plain chest films, a pericardial effusion of less that 150 ml may not distort the cardiac silhouette enough to be called abnormal. In fact, ultrasonographic studies have demonstrated that the number of patients with HD that have pericardial effusions is grossly underestimated.[13] Post-irradiation pericardial disease with effusions may occur if the field of irradiation includes the heart.

Of all the plain film studies, chest views are the most contributory to the management of HD. But patients may also have radiologic findings on plain films of the skeleton or abdomen. Bony lesions due to HD can result from direct lymphomatous invasion or by hematogenous tumor spread. These lesions are most commonly osteolytic or mixed osteolytic with a sclerotic border, and are ususally limited to the axial skeleton and proximal femur.[14] There is no correlation between the type of bony lesion seen on plain films and the histologic subtype of HD.[14] An "ivory vertebra" is consistent with HD. The phrase "ivory vertebra" is a descriptive radiologic term for a vertebral body that is homogenously radiopaque due to osteoblastic tumor activity.

The radiologic findings associated with HD on plain abdominal films are very non-specific. Gross lymphadenopathy may efface the lateral psoas margins or displace one or both kidneys. Iliac lymph node enlargement may be demonstrated as a thickening of the soft tissues of the pelvic wall. Splenomegaly or hepatomegaly may be evident on plain abdominal films but abdominal ultrasound, liver-spleen scans and computed tomography are much more sensitive in this regard.

Bipedal Lymphangiography (LAG)

The modern technique of LAG was developed by a surgeon, J.D. Kinnmonth, in 1952[15] and came into general use by 1959. Over the years, LAG has gained an important role in the assessment and staging of primary and secondary malignancies of the abdominal and pelvic lymphatic system. Prior to the maturation of LAG as a diagnostic and staging tool, excretory urography and inferior venacavography were used to assess abdominal and pelvic lymphadenopathy.

The high degree of accuracy of LAG in the assessment of abdominal and pelvic disease due to HD is well documented.[16] The limitations of LAG as a staging procedure are its medical contraindications, complications, cost, tediousness (both for the patient and radiologist) and inability to opacify all nodal groups in the abdomen and pelvis. Also the patient must refrain from movement for 1-1½ hrs. during the procedure. Presently, it has been thought that computed tomography should replace LAG as the primary abdominal staging procedure for patients with lymphoma.

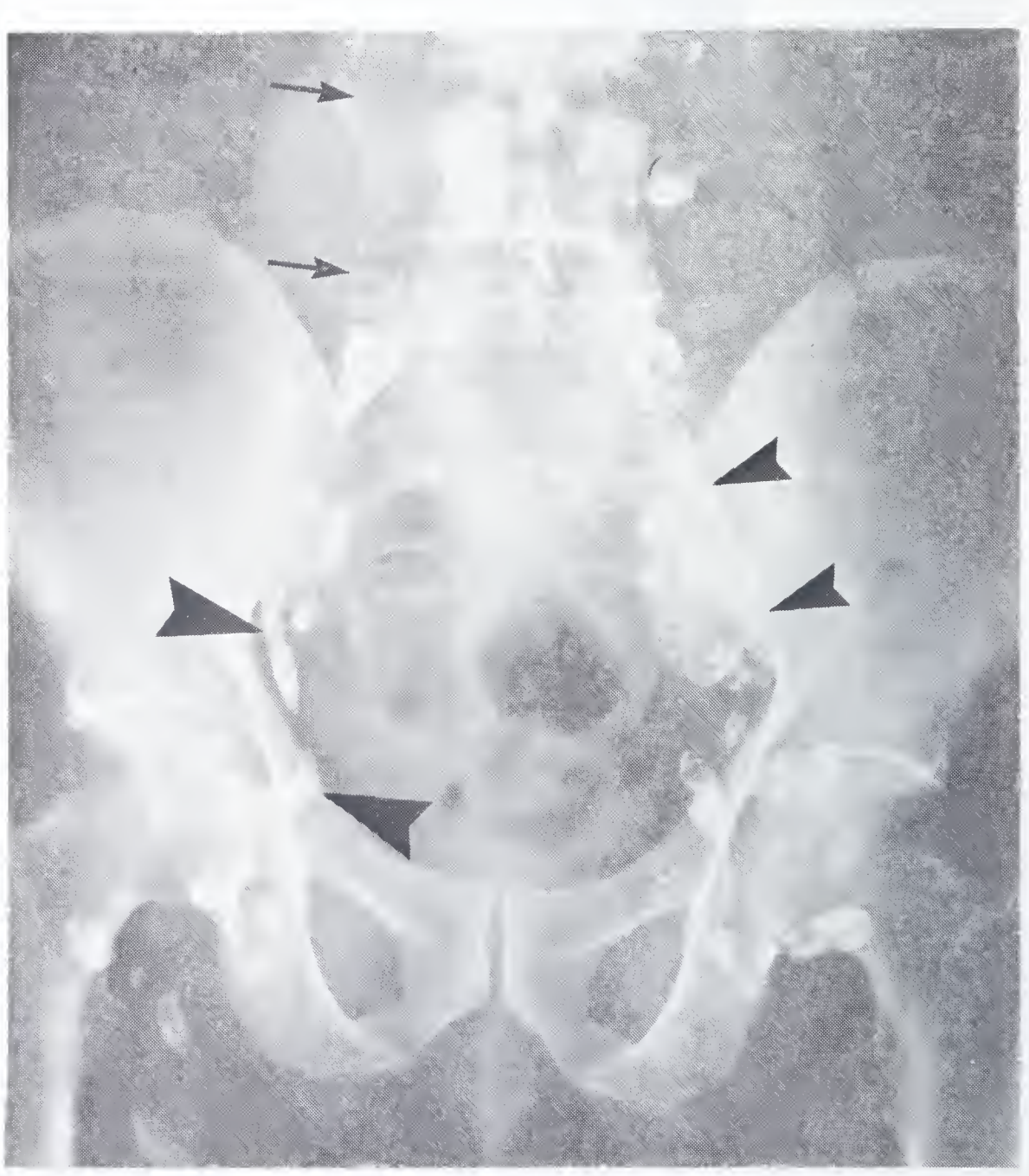

Fig. 3 Bipedal lymphangiogram: Plain film, of a patient with HD, taken 24 hrs. after bipedal injection of lymphographic contrast agent. The left external and left common iliac nodes are enlarged and foamy (small arrowhead). The right common iliac and right para-aortic nodes are enlarged and show large filling defects (arrows). For comparison, the right iliac nodes and right pelvic nodes are of normal size and architecture (large arrowheads).

The following is an outline of a typical LAG.

1. A vital dye (e.g. patent blue violet) is injected, subcutaneously and intradermally, into the first and second interdigital spaces. Because the dye is selectively absorbed by lymphatic vessels, blue streaks appear on the dorsum of each foot.
2. Under local anaesthetic, a cutdown is done on one of the blue streaks, thus exposing a lymphatic vessel.
3. The lymphatic vessel is cannulated and a lymphographic contrast agent is injected into the cannulated vessel. The lymphographic contrast agent in most common use is Ethiodol, an iodinated derivative of poppy seed oil.
4. Plain films of the legs, pelvis and abdomen are taken immediately after contrast injection to visualize the lymphatic phase of the LAG.
5. Twenty-four hours after contrast injection, plain films are taken of the abdomen and pelvis to demonstrate the nodal phase of the LAG.

Ethiodol is retained in lymph nodes for a variable time from six months to two years, so plain films of the abdomen can be used to monitor the response of diseased nodes to therapy and detect progression or recurrence of HD.

In 1967, Takahashi and Abrams reviewed the lymphographic criteria for lymph nodes infiltrated by lymphoma.[17] These criteria are: foamy nodes, filling defects occupying more than one-third of the node, para-aortic nodes greater than 2.6 cm in size, anterior extension of nodes greater than 3 cm from the anterior aspect of the vertebral bodies and lateral displacement of nodes greater than 2 cm from the concave border of the adjacent vertebral body. (Fig. 3). It must be remembered that abnormal findings on a lymphographic study are never pathognomonic of a specific disease process.

The foaminess and filling defects seen in lymph nodes involved by HD are due to replacement of normal nodal tissue by tumor. An indentation in a node caused by the hilus of the node can be mistaken for a filling defect. The location of the hilum of a node can be seen on films of the lymphatic phase. In older patients, anterior and/or lateral displacement of nodes about the vertebral column may be caused by a tortuous aorta.

An advantage of LAG over other abdominal staging procedures such as computed tomography and ultrasound is that the internal architecture of lymph nodes can be demonstrated by LAG. Lymph nodes are recognized to be abnormal by computed tomography and ultrasonography only if they are enlarged.

A typical LAG demonstrates inguinal, pelvic and paralumbar nodes. Certain nodal groups cannot be examined by LAG, including the internal iliac nodes, retrocrural and high para-aortic nodes, presacral nodes, mesenteric nodes, splenic hilar nodes and nodes at the porta hepatis. As well, the size and texture of the liver and spleen cannot be accurately assessed by LAG.

The most common complications of a LAG are: allergic reactions to the vital dye or the iodine component of Ethiodol, pneumonitis, pulmonary embolism and a local infection at the site of contrast injection. The pulmonary complications are due to the fact that the oil-based lymphographic contrast agent eventually reaches the pulmonary circulation by way of the thoracic duct and right heart. There have been reported cases of systemic arterial oil emboli, following LAG, due to an unknown pre-existing right-to-left cardiac shunt.[18]

The absolute contraindications to LAG are: severe pulmonary disease, a-v fistulae, right-to-left shunts, a previous allergic reaction to an iodinated radiographic contrast agent or the vital dye and known lymphatico-venous communications. Relative contraindications to LAG are predisposition to infection and previous radiotherapy or surgery involving the major lymphatics of interest. Radiation or surgery can create lymphatico-venous communications resulting in large pulmonary oil emboli.

Computed Tomography (CT)

Since the advent of whole-body computed tomography in 1975, CT has played an ever-increasing role in the staging and follow-up of patients with abdominal, pelvic and thoracic manifestations of HD.

A typical CT examination of the abdomen and pelvis consists of slices of 1 cm thickness taken at 1-2 cm intervals from the xyphoid process to the symphysis pubis. Slices can be taken at smaller intervals in areas of specific interest. An oral contrast agent (e.g. gastrograffin) is given before the procedure and at the time of the examination to opacify the stomach and bowel loops. Intravenous contrast can be given during the examination to enhance the appearance of vascular structures. Artifacts on CT examination of the abdomen and pelvis can arise from surgical clips, metallic orthopedic devices, respiration, cardiac pulsations and patient movement.

By CT, one can image virtualy all the main nodal groups in the abdomen and pelvis. The para-aortic, retrocaval, paracaval and retrocrural nodes are easily identified in most patients because they are surrounded by fat. It may be difficult to demonstrate these nodal groups in a thin or cachectic patient. Pelvic lymph nodes are more difficult to assess than abdominal nodes because of their variable location, size and transaxial CT plane orientation. Pelvic lymphadenopathy may be detected on CT due to an asymmetry of the neurovascular bundles on the pelvic wall.

The resolution possible with contemporary CT machines makes it impossible to visualize internal nodal architecture. Thus, for a node to be called abnormal on CT examination it must be enlarged. Lymphadenopathy due to HD can present on CT either as discrete structures or as a homogenous mass. Lymph nodes in the para-aortic, retrocaval and paracaval groups are considered pathological if they exceed 2.0 cm in diameter or if there are an increased number of nodes greater than 1.0 cm in diameter.[19] Displacement or obliteration of normal structures, such as the psoas muscles, aorta, kidneys and inferior vena cava, is consistent with retroperitoneal lymphadenopathy. Para-aortic lymphadenopathy may displace the aorta anteriorly, causing the "floating aorta sign".[20] (Fig. 4). Normal retrocrural structures include lymph nodes, azygos vein, thoracic duct or cisterna chyli and nerves. A retrocrural structure greater than 6 mm in diameter is considered abnormal and is consistent with retrocrural lymphadenopathy.[21]

One must be aware of normal structures that may mimic lymphadenopathy on CT of the abdomen or pelvis. The right crus of the diaphragm often has a round contour and may be mistaken for retrocaval lymphadenopathy. An enlarged left gonadal vein or duplicated IVC can be differentiated from

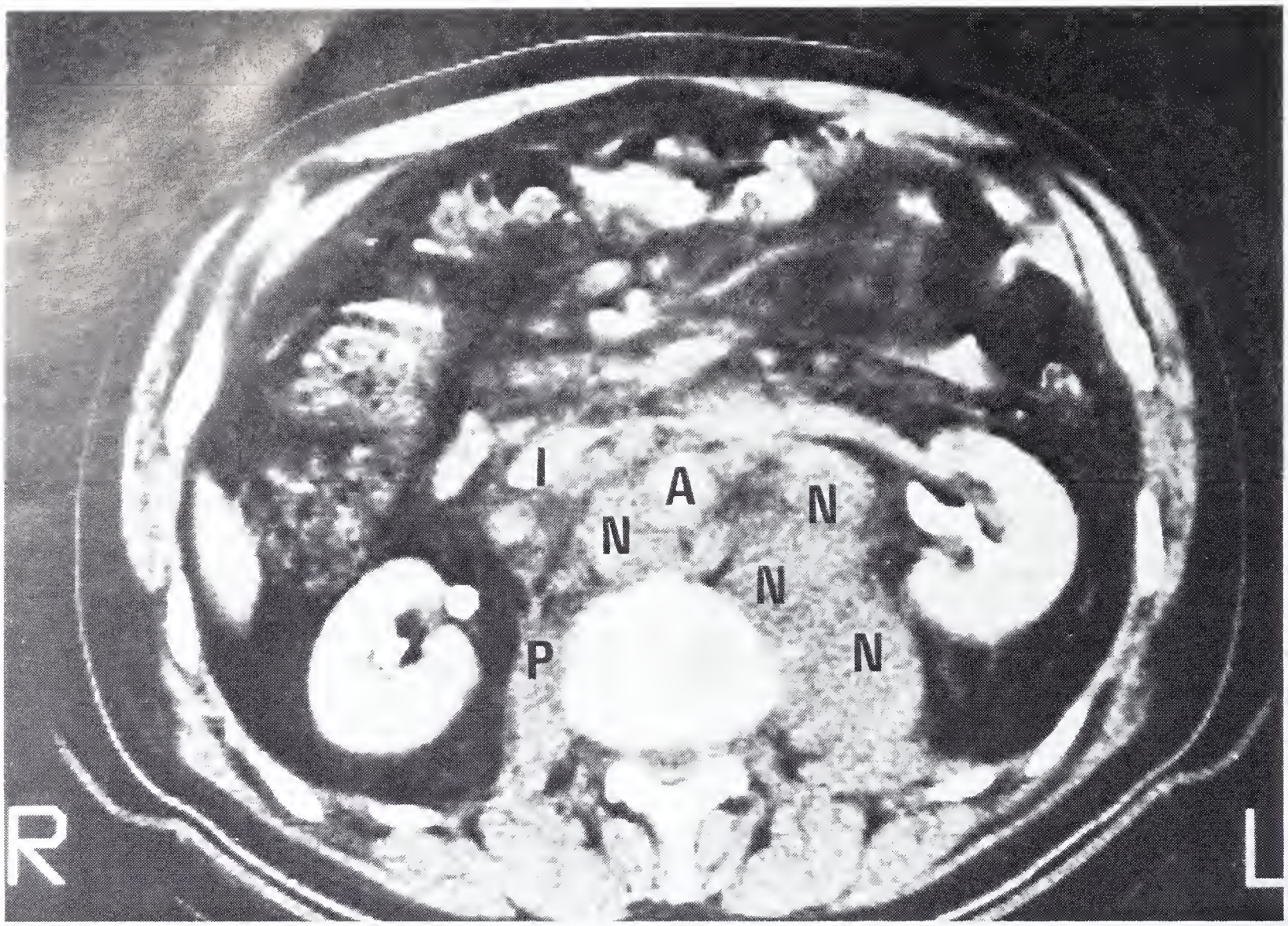

Fig. 4 CT scan of the abdomen at the level of the left renal hilum of a patient with HD. There is extensive lymphadenopathy involving the retrocaval and para-aortic nodes with obliteration of the left "psoas" margin and antero-lateral displacement of the left kidney. The aorta has been displaced anteriorly, creating the "floating aorta sign". Intravenous contrast can be seen in the pelvis and ureter of both kidneys. Oral contrast (gastrografin) was given to opacify bowel loops. Aorta (A), IVC (I), Right psoas muscle (P), Areas of lymphadenopathy (N).

Fig. 5 Sagittal tomogram of the lumbar spine centered at L2 (arrow) of a patient with Stage IV HD. The abnormal sclerotic (osteoblastic) vertebral body characterizes the radiological descriptive term of an "ivory vertebra".

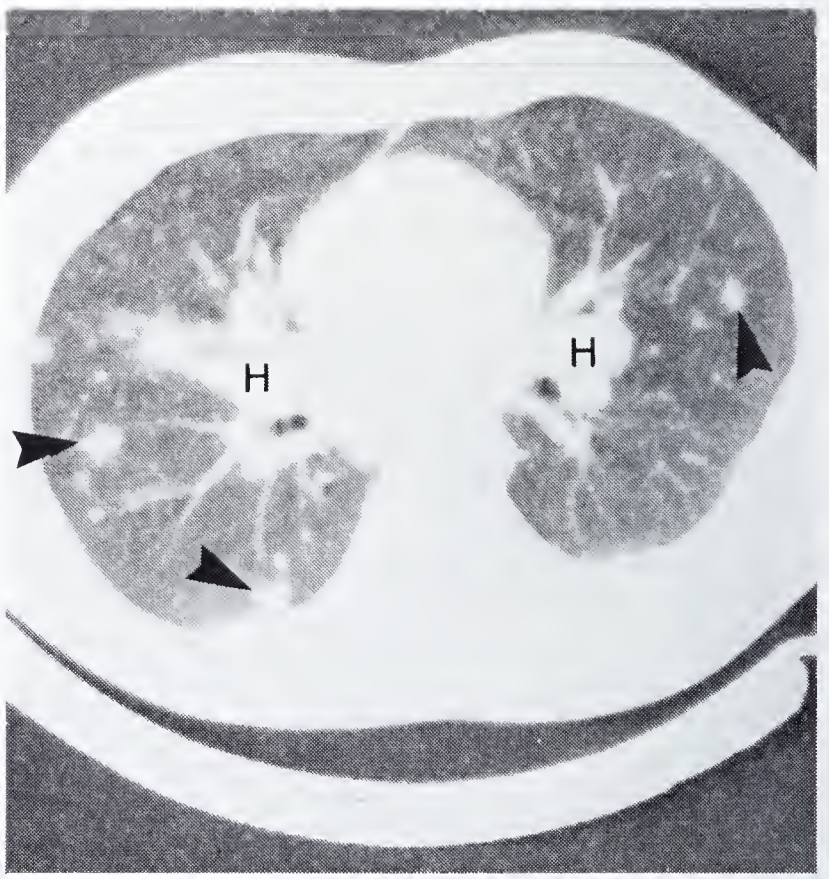

Fig. 6 CT scan of the thorax, at the subcarinal level, of a patient with Stage IV HD. Shown is bilateral hilar enlargement (H) due to lymphadenopathy and multiple pulmonary lymphomatous deposits (arrows).

lymph nodes by the administration of intravenous contrast. Bowel loops not opacified by the oral contrast agent may mimic lymphadenopathy.

CT is insensitive and shows a low overall accuracy in detecting splenic and hepatic involvement by Hodgkin's Lymphoma.[22] There are no strict CT criteria for hepatomegaly or splenomegaly. In most instances, the radiologist makes the observation of organomegaly based on experience, not specific measurements. CT is much more sensitive than clinical assessment in the detection of splenomegaly. However, splenic or hepatic involvement by HD may not cause organomegaly. Diffuse tumor infiltration of the spleen and small intrasplenic tumor nodules cannot be detected by CT. Hepatic lymphoma is difficult to detect by CT because it is usually confined to the portal triad and presents as small foci of tumor.[22] It is interesting that one-third of patients with HD and splenomegaly have no pathologic evidence of HD within the spleen.[23]

The detection of lymphomatous involvement of the spleen or liven often alters the stage and treatment of the patient. Splenic lesions can be the only abdominal presentation of HD. Thus, CT cannot be employed as the sole method of splenic and hepatic assessment in a patient with HD.

Plain films, conventional tomography and radioisotopic bone scans are usually sufficient for the detection and assessment of bony lesions due to HD (Fig. 5). However, CT is often necessary to determine the local extent of these lesions.

The application of CT to the investigation of thoracic disease is relatively new. Scans are taken with the breath held in full inspiration. Intravenous contrast can be given to delineate the great vessels. With respect to HD, CT of the thorax has been useful in the investigation of apparent mediastinal widening on plain chest films and in the detection of occult pulmonary nodules and lymphomatous involvement of the chest wall. CT is more sensitive than plain films and routine whole-lung tomography for the detection of small pulmonary tumor nodules.[24] The detection of small pulmonary nodules distinct from the hila makes the patient an Ann Arbor Stage IV and may alter the prognosis and therapy. (Fig. 6).

Ultrasound (US)

Ultrasound (US) has a limited but definite contribution to make to the staging and follow-up of abdominal and pelvic due to HD.

Like computed tomography (CT), a lymph node can only be recognized as abnormal on ultrasonographic examination if it is enlarged. In general, lymphadenopathy presents on US as an echo-poor mass with good acoustical transmission. (Fig. 7). It may be confused with cysts or fluid-filled bowel loops.

In a preliminary study done by the author, US was shown to be insensitive, compared to CT and LAG, in the detection of intra-abdominal and intra-pelvic lymphadenopathy. Ultrasound is best at detecting bulky lymphomatous disease.

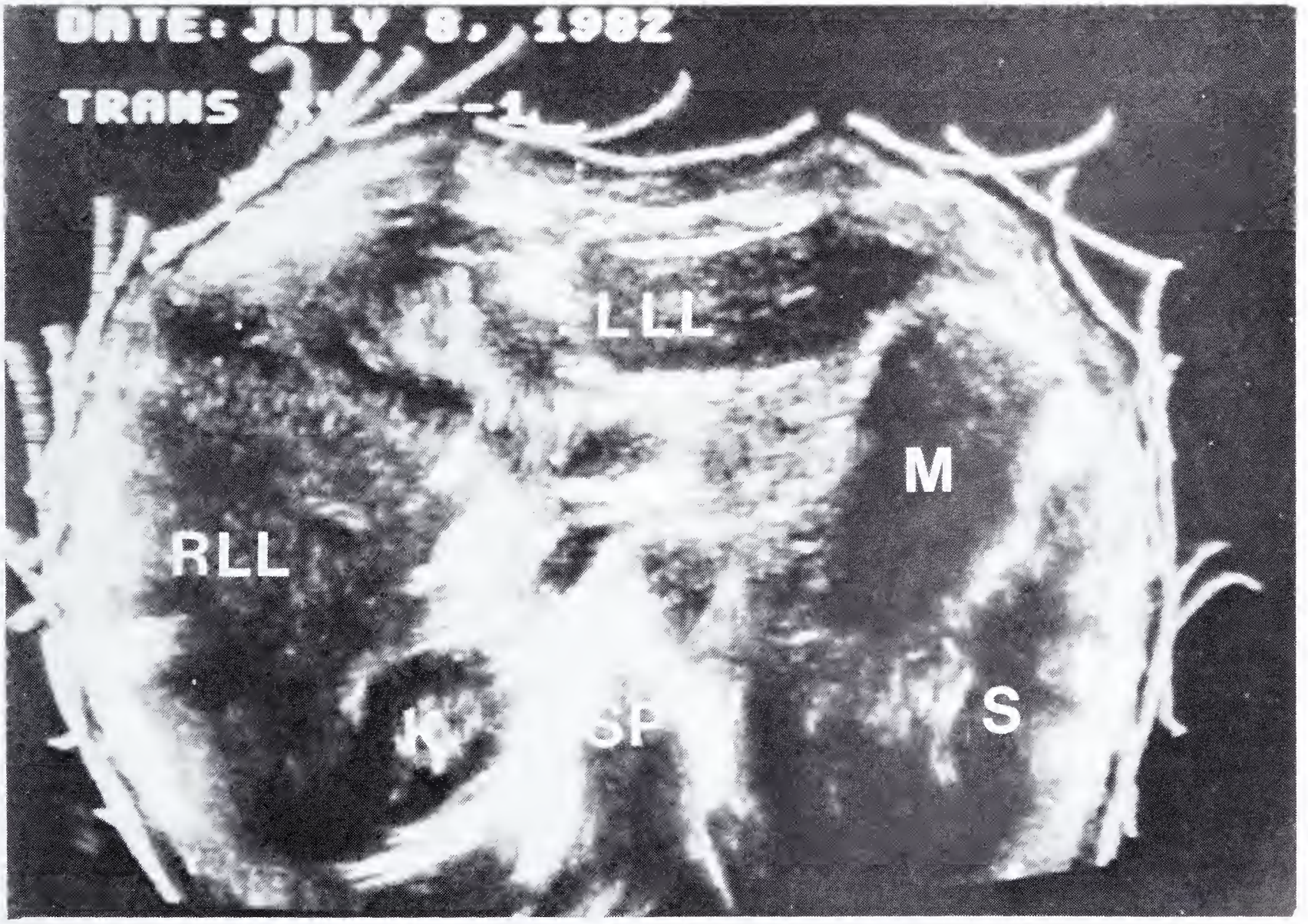

Fig. 7 Ultrasonographic transverse section of the abdomen of a patient with lymphocyte-depleted HD. Shown is a large lymphomatous mass (M) in the LUQ of the abdomen. The mass was clinically palpable and responded to chemotherapy and radiotherapy. Right lobe of liver (RLL), Left lobe of liver (LLL), Right kidney (K), Spleen (S) and Spine (SP).

Overlying bowel gas often prevents adequate visualization of nodes in the mid-to-lower abdomen and pelvis. A good visualization of retroperitoneal structures may be difficult in an obese patient.

Extranodal abdominal or pelvic involvement by HD may be detected on US. The size of the liver and spleen can be estimated and echo-poor lymphomatous lesions in these organs may be visualized. Suspected biliary tract obstruction or obstructive uropathy due to lymphadenopathy can be easily confirmed by ultrasound.

Nuclear Medicine

The nuclear scans presently used to assess a patient with HD are gallium, bone and liver-spleen scans.

Gallium scanning is a non-specific radioisotopic study that aids in the localization of lymphomatous tumor involvement. The patient receives an intravenous injection of 6-8 mCi of ^{67}Ca citrate and is scanned 72 hours later. The ^{67}Ga is normally concentrated in the axial skeleton and shoulder joints, nasopharynx, breast tissue, liver and spleen.[25] Normal lymph nodes show no uptake of ^{67}Ga. Twenty-four hours after injection of the radiopharmaceutical, the large bowel becomes the major route of excretion. Visualization of tumor is dependent on local blood flow, tumor affinity and a leaky tumor microvasculature. In a study by Alexander Gottschalk, ^{67}Ga citrate and is scanned 72 hours later. The ^{67}Ga is normally concentrated in the axial skeleton and shoulder joints, time for abdominal disease.[25] The uptake of gallium in the colon, liver and spleen interferes with the detection of retroperitoneal disease.

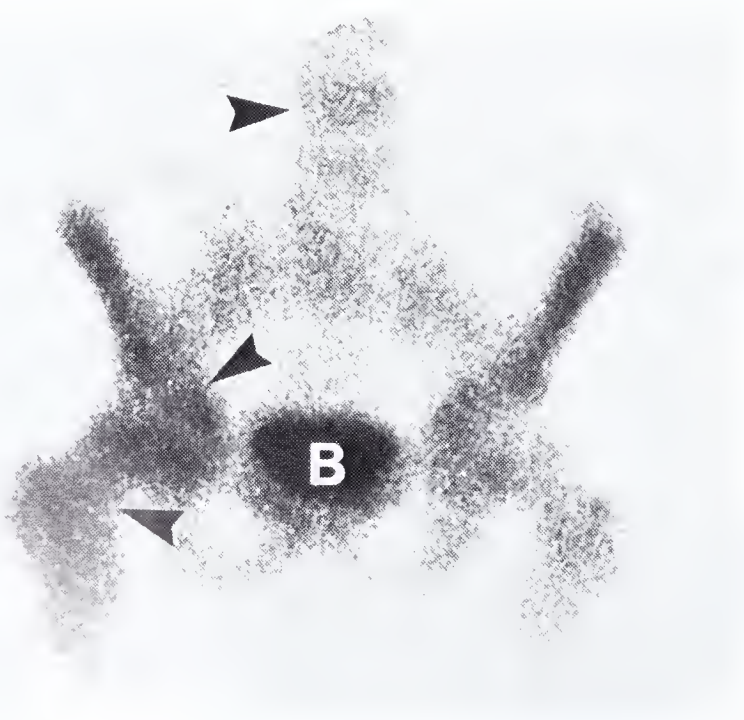

Fig. 8 Technetium-99m bone scan of a patient with HD. The anterior surface of the patient is closest to the gamma camera. There is increased uptake in the right proximal femur, right acetabulum and L4 vertebra (arrows). The left proximal femur, left acetabulum and the right and left iliac crests show normal uptake. The bladder is "hot" (B) because the radiopharmaceutical is excreted by the kidneys.

In the study of HD, bone scans are used to detect lymphomatous lesions of the skeleton. In HD, bony lesions are most common in the axial skeleton and proximal femur (Fig. 8). The radioisotope in present use is 99m-Technitium. Increased uptake in bone may be due to an increased blood flow, increased bone formation or marked bone turnover. Some conditions associated with an increased bony uptake of 99m-Tc are: benign or malignant tumors, infection, infarction, Paget's Disease and fracture. A bone scan often detects lesions before they are evident on plain films.

Liver-spleen scans are performed on patients with HD to assess the liver and spleen size and detect hepatic or splenic lymphomatous lesions. A 99cm-Tc labelled sulphur colloid is injected intravenously and is phagocytosed by the reticular endothelial system. The liver-spleen scan can detect hepatosplenomegaly, focal defects in uptake a few centimetres in diameter and an uptake pattern that suggests diffuse infiltration of the liver or spleen by tumor.

Conclusion

The contributions of various radiological modalities to the detection and localization of lymphomatous involvement due to Hodgkin's Disease have been reviewed. Today, patients with HD have a significantly better prognosis than in the past. Therapy depends on the stage and location of the disease. In defining the stage and precise location of the tumor, imaging techniques are of paramount importance for the successful management of a patient with HD. □

Acknowledgements

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References

1. Hodgkin, T.: On Some Morbid Appearances of the Absorbent Glands and Spleen. *Medico-Chirurgical Transactions 17*:68-114, 1832.
2. Haskell, C.M.: Cancer Treatment. W.B. Saunders Co. Toronto, 1980, Chapter 24.
3. Kaplan, H.S.: Hodgkin's Disease. Harvard University Press, Cambridge, Mass., 1972.
4. Beretta, G. *et al.*: Sequential laparoscopy and laparotomy combined with bone marrow biopsy in staging Hodgkin's Disease. *Cancer Treat. Rep. 60:*1231, 1976.
5. Lukes, R.J. *et al.*: Report of the Nomenclature Committee. *Cancer Res. 26:*1311, 1966.
6. Smithers, D.: Hodgkin's Disease. Churchill Livingstone, London, 1973.
7. Ultmann, J.E. and Moran, E.M.: Hodgkin's Disease: Clinical course and complications. *Arch. Intern. Med. 78:*113, 1973.
8. Newal, J.: The management of Hodgkin's Disease. *Clin. Radiol. 16:*40-50, 1965.
9. Kaplan, H.S.: Hodgkin's Disease and other human malignant lymphomas. Advances and prospects — G.H.A. Clowes Memorial Lecture. *Cancer Res. 36:*3863, 1976.

10. Filly, R. *et al.*: Radiographic distribution of intrathoracic disease in previously untreated patients with Hodgkin's Disease and Non-Hodgkin's Lymphoma. *Radiology 120*:277-281, 1976.

11. Blank, N., Castellino, R.A.: the Intrathoracic Manifestations of the Malignant Lymphomas and Leukemias. Seminars in Roentgenology: The Lymphomas and Leukemias, Part 1. July 1980.

12. Weick, J.K. *et al.*: Pleural effusion in lymphoma. *Cancer 31*:848-853, 1973.

13. Markiewicz, W. *et al.*: Echocardiographic detection of pericardial effusion and pericardial thickening in malignant lymphoma. *Radiology 123*:161-164, 1977.

14. Beachley, M.C. *et al.*: Bone involvement in Hodgkin's Disease. *Am. J. Roentgenol. Radium Ther. Nucl. Med. 114*:559-563, 1972.

15. Kinnmonth, J.D.: Lymphangiography in man. A method of outlining lymphatic trunks at operation. *Clin. Sci. 11*:13-20, 1952.

16. Marglin, S., Castellino, R.: Lymphographic accuracy in 632 consecutive, previously untreated cases of Hodgkin's Disease and Non-Hodgkin's Lymphoma. *Radiology 140*:351-353, 1981.

17. Clouse, M.E.: Clinical Lymphography. Golden's Diagnostic Radiology: Section 7. Williams & Wilkins, Baltimore, 1977.

18. Davidson, J.W.: Lipid embolism to the brain following lymphography. *Am. J. Roentgenol. 105*:763-771, 1969.

19. Lee, J.K.T. *et al.*: Accuracy of computed tomography in detecting intra-abdominal and pelvic adenopathy in lymphoma. *Am. J. Roentgenol. 131*:311, 1978.

20. Havrilla, T.R. *et al.*: The floating aorta in computerized tomography: a sign of retroperitoneal pathology. *Comp. Axial Tomogr. 1*:107, 1977.

21. Callen, P.W. *et al.*: Computed Tomographic Evaluation of the Retrocrural Prevertebral Space. *Am. J. Roentgenol. 129*:907-910, Nov. 1977.

22. Jones, S.E. *et al.*: Computed Tomographic Scanning in patients with lymphoma. *Cancer 41*:480-486, 1976.

23. Kadin, M.E. *et al.*: Clinicopathologic studies in 177 untreated patients subjected to laparotomy for staging of Hodgkin's Disease. *Cancer 27*:1277-1294, 1971.

24. Schaner, E.G. *et al.*: Comparison of computed and conventional whole lung tomography in detecting pulmonary nodules: a prospective radiologic-pathologic study. *Am. J. Roentgenol. 131*, 51, 1978.

25. Gottschalk, A.: Tumor Scanning of Lymphomas. Diagnostic Nuclear Medicine, Golden's Diagnostic Radiology, Williams & Wilkins Co., Baltimore, 1976.

Shattered Dreams

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COMMENTARY

With The Eye Of Faith

Murray Rosenbaum 8T5

"It is a great pleasure for me to be lecturing to you today". This is a phrase heard not infrequently in the lecture halls of the medical sciences building. But what does the lecturer really mean when he or she uses this or other famous, well used and abused statements. In this case, the lecturer is probably really saying, "lecturing to medical students means being affiliated with the University of Toronto medical school, and that looks great on my record." I would like to look at a few more, interesting yet misunderstood comments lecturers make.

"Can we have the next slide, please. With the eye of faith you can see the paler area in here . . ." What the lecturer actually means is that the lesion is supposed to be there, but even if we can't see it, let's say we can. Thus, the students are asked to use their imagination. Thus, part of medicine is taught on the basis of belief and imagination — the same basis as the Mr. Rogers show (a T.V. show for children). "Can you see the furry little dragon in your teapot?" asks Mr. Rogers. "Can you see the well demarcated lesion?" asks the lecturer. Strangely enough, there is the odd student who does see the imaginary lesion. This is the same student who hears the grade 0.1 out of 6 murmur which only the clinician hears.

It is interesting to note how lecturers deal with questions. When their response to a question is, "good question!," it could mean a few things. A *differential interpretation* would include the following:

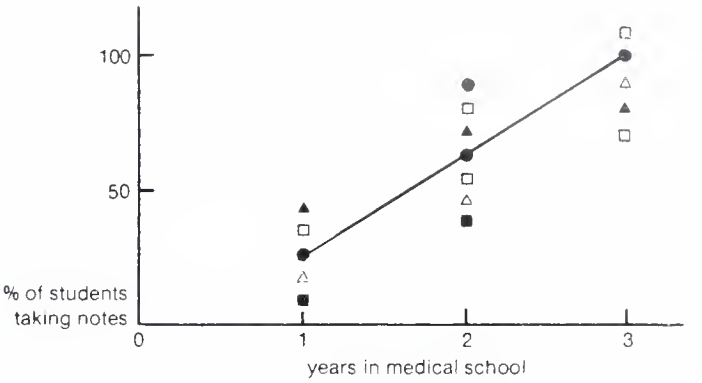
"I never thought of that one,"
"excellent thought, I don't know the answer,"
"picky, picky, picky!"

A more vague response to a question is, "speak to me after class." The true meaning here could be many different things. A few which come to mind are:

"that's the dumbest question I've ever heard,"
"too much bother to answer,"
"if I tell you to ask me later, maybe you'll forget,"
"you'll never find me after the class."

Scepticism always follows the opening statement, "I just want you to understand the basics." Here is a case of a misinterpretation by the unwary student only because the statement is incomplete. It should read: "I just want you to understand the basics, *but* the test will cover all the trivial details dealt with in Harrison's p. 1190-1210."

I will end with a study on the famous last words, "put your pens down and listen, it's all in the handout." The intent of these words is obvious; they represent the most deceitful tactic of lecturers. On occasion, the information is in the handout* but usually it is not. It is this inconsistency which leaves some students in doubt. The study to which I have eluded plots student response to this remark. There is a definite correlation between the years of medical school experience and trust/mistrust. The level of trust cannot be measured directly. However, the level of trust is inversely proportional to the percentage of students taking notes subsequent to this comment. These are the results:



We find a linear increase in percentage of note taking, reflecting a decrease in student trust. The basic principle here is that you can't fool all of the students all the time by third year.

Initial student reaction to this remark may be applause or pen dropping, as time goes on, this comment may be greeted by intense hissing or booing. Finally, in third year, the reaction is most likely to be, "got any extra paper, I'd better get this down."

Students are beginning to catch on to the curve balls thrown at them by lecturers. The crafty third years can see through these puerile little games, so, lecturers, take heed! Either you play it honest, or think of new tricks, but remember, tricks are for kids. We students aren't here to play games, we came here "because we like helping people."□

* When the information is, in fact, in the handout, usually the students aren't notified.

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Photo credit: T. Draimin

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War, hunger and oppression are in the headlines. Bad as it all is...there is hope. The refugees have an untold story of strength, ingenuity and self-reliance.

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Dalacin® C Phosphate Phosphate S.S.

Recommended Applications

Action: Clindamycin exerts its [illegible]terial effect by causing cessation of protein synthesis and also by causing a reduction in the [illegible] synthesis of nucleic acids.

Indications: Dalacin C Phosphate (clindamycin phosphate) is indicated for the treatment of infections where the oral route is not indicated or feasible

Dalacin C Phosphate is indicated in the treatment of serious infections due to sensitive anaerobic bacteria such as Bacteroides species peptostreptococcus, anaerobic streptococci, Clostridium species and microaerophilic streptococci

Dalacin C Phosphate is also indicated in serious infections due to sensitive Gram-positive organisms (staphylococci including penicillinase-producing staphylococci, streptococci and pneumococci) when the patient is intolerant of or the organism resistant to other appropriate antibiotics

Contraindications: The use of Dalacin C Phosphate (clindamycin phosphate) is contraindicated in patients previously found to be hypersensitive to this compound the parent compound, clindamycin or clindamycin palmitate Although cross-sensitization with Lincocin® (lincomycin hydrochloride) has been demonstrated it is recommended that Dalacin C Phosphate not be used in patients who have demonstrated lincomycin sensitivity

Until further clinical experience is obtained, Dalacin C Phosphate is not indicated in the newborn (infants below 30 days of age), or in pregnant women

Warnings: Some cases of severe and persistent diarrhea have been reported during or after therapy with Dalacin C Phosphate (clindamycin phosphate) This diarrhea has been occasionally associated with blood and mucus in the stools and has at times resulted in acute colitis When endoscopy has been performed, some of these cases have shown pseudomembrane formation.

If significant diarrhea occurs during therapy, this drug should be discontinued or, if necessary, continued only with close observation Significant diarrhea occurring up to several weeks post-therapy should be managed as if antibiotic-associated.

If colitis is suspected, endoscopy is recommended Mild cases showing minimal mucosal changes may respond to simple drug discontinuance Moderate to severe cases, including those showing ulceration or pseudomembrane formation, should be managed with fluid, electrolyte, and protein supplementation as indicated Corticoid retention enemas and systemic corticoids may be of help in persistent cases Anticholinergics and antiperistaltic agents may worsen the condition Other causes of colitis should be considered

Studies indicate a toxin(s) produced by Clostridia (especially Clostridium difficile) may be a principal cause of clindamycin and other antibiotic-associated colitis. These studies also indicate that this toxigenic Clostridium is usually sensitive *in-vitro* to vancomycin When 125 mg to 500 mg of vancomycin were administered *orally* four times a day for 5 – 10 or more days, there was a rapid observed disappearance of the toxin from faecal samples and a coincidental recovery from the diarrhea

It should be noted that serious relapses have occurred up to one month after apparently successful treatment A relatively prolonged period of continuing observation is therefore recommended

Precautions: Dalacin C Phosphate (clindamycin phosphate), like any drug, should be prescribed with caution in atopic individuals

Dalacin C Phosphate must be diluted for intravenous administration (See Dosage and Administration)

The use of antibiotics occasionally results in overgrowth of nonsusceptible organisms – particularly yeasts Should superinfections occur, appropriate measures should be taken as dictated by the clinical situation

As with all antibiotics, perform culture and sensitivity studies in conjunction with drug therapy

Since abnormalities of liver function tests have been noted occasionally in animals and man, periodic liver function tests should be performed during prolonged therapy Blood counts should also be monitored during extended therapy

Dalacin C Phosphate may be used in anuretic patients. Since the serum half-life of clindamycin in patients with impaired hepatic function is greater than that found in normal patients, the dose of Dalacin C Phosphate should be appropriately decreased Hemodialysis and peritoneal dialysis are not effective means of removing the compound from the blood Periodic serum levels should be determined in patients with severe hepatic and renal insufficiency

Adverse **Reactions:** *Local*

(a) *Intramuscular Injections* Of 404 patients treated with Dalacin C Phosphate (clindamycin phosphate) intramuscularly (with a solution containing 150 mg/mL), six (1.5%) demonstrated local reactions as follows Two complained of pain at the injection site, two demonstrated induration at the injection site and two developed sterile abscesses

(b) *Intravenous Infusions*. Of 192 patients treated with Dalacin C Phosphate by intravenous infusion, 14 (7.3%) demonstrated local reactions. Eleven patients developed superficial thrombophlebitis and one patient developed both superficial and deep thrombophlebitis. The majority of these cases developed in conjunction with the use of indwelling I.V. catheters and it is difficult to know how much the drug contributed to the irritation Two patients developed localized erythema, swelling and pain at the site of the infusion.

Systemic Side Effects: Twenty-eight patients of 596 treated with Dalacin C Phosphate (clindamycin phosphate) by either the intramuscular or intravenous routes developed systemic side effects as follows.

	Number of Patients
Rash	7
Urticaria	1
Pruritus	1
Fever Leucocytosis	1
Nausea with or without vomiting	1
[illegible]arrhea (See also under 'Warnings')	4
[illegible]	1
[illegible]	1
[illegible] of Breath	1
[illegible]*	4
Cardia[illegible]**	1
[illegible] in mouth	5

*Sube[illegible] complication of antibiotic therapy in general and is not necessarily a true side effe[illegible]damycin phosphate

**Due to [illegible] myocardits in this patient

Clinical and Laboratory Findings: Patients treated during clinical trials of Dalacin C Phosphate (clindamycin phosphate) were followed with clinical laboratory tests, including complete hematology, urinalysis and liver and kidney function tests. Some of these tests were abnormal initially and returned to normal during therapy with Dalacin C Phosphate, while others were normal initially and became abnormal during therapy Overall evaluation of clinical laboratory values in these patients does not indicate that Dalacin C Phosphate therapy has a toxic effect on the hematopoietic, hepatic or renal systems. Transient elevations of serum transaminases have occurred in some patients, but other liver function tests (alkaline phosphatase, serum bilirubin) have not shown any tendency to increase and there have not been clinical signs of drug-induced hepatic toxicity.

Symptoms and Treatment of Overdosage: No cases of overdosage have been reported No specific antidote is known Doses as high as 1200 mg every six hours (4800 mg/day) by infusion for five days have been given without adverse effects.

DOSAGE AND ADMINISTRATION

Adults

Intramuscular Injection. 600 mg/day in 2 equal doses.

Moderately severe infections: 600 to 1200 mg/day in 2 or 3 equal doses.

Severe infections 1200 to 2400 mg/day in 2, 3 or 4 equal doses. Intramuscular injections of more than 600 mg into a single site are not recommended

Intravenous Administration: Dalacin C Phosphate (clindamycin phosphate) must be diluted prior to I.V. administration to a dilution of 300 mg in 50 ml of diluent (6 mg/ml) or more, and infused in not less than 10 minutes. Administration of more than 1200 mg in a single 1 hour infusion is not recommended Dalacin C Phosphate should not be injected intravenously undiluted as a bolus

Moderately severe infections 900 to 1800 mg/day by continuous drip or in 2 or 3 equal doses, each infused over 20 minutes or longer

Severe infections 1800 to 2700 mg/day by continuous drip or in 3 or 4 equal doses, each infused over 20 minutes or longer. In life-threatening infections, doses of 2700 to 4800 mg/day by continuous drip or in 3 or 4 equal doses each infused over 20 minutes or longer may be given

Dilution and infusion rates:

Dose	*Diluent*	*Time*
300 mg	50 ml	10 min
600 mg	100 ml	20 min
900 mg	150 ml	30 min
1200 mg	200 ml	45 min

Alternatively, drug may be administered in the form of a single rapid infusion of the first dose followed by continuous I.V. infusion as follows:

To maintain serum clindamycin levels	*Rapid infusion rate*	*Maintenance infusion rate*
Above 4 mcg/ml	10 mg/min. for 30 min	0.75 mg/min
Above 5 mcg/ml	15 mg/min. for 30 min	1.00 mg/min.
Above 6 mcg/ml	20 mg/min. for 30 min.	1.25 mg/min

Children: (Over one month of age)

Intramuscular injection 10 to 15 mg/kg/day in 2, 3 or 4 equal doses.

Moderately severe infections 15 to 20 mg/kg/day in 3 or 4 equal doses.

Severe infections 20 to 30 mg/kg/day in 3 or 4 equal doses

Intravenous Administration:

Moderately severe infections 15 to 25 mg/kg/day by continuous drip or in 3 or 4 equal doses, each infused over 20 minutes or longer. In severe infections, it is recommended that children be given no less than 300 mg/day regardless of body weight (Dilute Dalacin C Phosphate Sterile Solution in the same manner as for adults)

Dilution and Compatibility:

4 ml (600 mg) Dalacin C Phosphate when diluted with 1000 ml of the following commonly used infusion solutions was found to be physically compatible and demonstrated no significant change in pH or antimicrobial potency over a period of 24 hours.

Sodium chloride injection
Dextrose 5% in water
Dextrose 5% in saline
Dextrose 5% in Ringer's Solution
Dextrose 5% in half-strength saline plus 40 mEq potassium chloride
Dextrose 2½% in Lactated Ringer's Solution (Hartmann's Solution)

Dalacin C Phosphate was not stable when added to Dextrose 5% in water plus vitamins. Therefore it is not recommended that Dalacin C Phosphate be mixed with any infusion solution containing B vitamins.

Supplied:

Dalacin C Phosphate contains the following per ml of sterile solution.

Clindamycin phosphate equivalent to clindamycin base 150 mg
Benzyl alcohol 5 mg
Disodium edetate 0.5 mg
Water for injection q.s

When necessary the pH is adjusted with sodium hydroxide and/or hydrochloric acid to maintain a pH range of 5.5 to 7.0

Dalacin C Phosphate is available in 2 ml and 4 ml ampoules

NOTE: Do not store below 15°C.

Product Monograph available upon request. CE 1377 1C

834 [illegible]GISTERED TRADEMARK DALACIN TRADEMARK DALACIN C CE 3692 1L (CE 709)

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(clindamycin phosphate)

...the standard to which others are compared.

- Provides excellent penetration into infected abscesses.[2]
- Highly effective against gram-positive aerobes including penicillinase – producing Staphylococci.
- Highly effective against gram-positive and gram-negative anaerobes, in particular *Bacteroides fragilis.*
- After 10 years of clinical use, resistance development to *Bacteroides fragilis* is as low as 2%.[3]
- Has *never* been associated with any carcinogenic or mutagenic activity.
- May enhance the natural host defense system; has been shown to concentrate within polymorphonuclear leukocytes in vitro. These neutrophils in turn may act as an important antibiotic delivery system to the site of infection.[4]

1. R. Fekety, M.D., Drug Therapy Hospital, October 1982
   *In combination with an aminoglycoside.
2. Mouzas G.L., et al (1980) Brit J Clin Pract *34*:234
3. M.H. Yee, M.D. et al, JAMA, October 15, 1982, Vol. 248, No 15
4. M.S. Klempner et al, J. Inf. Dis., Vol. 144, No. 5, November 1981

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